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Textbook of Addiction Treatment: International Perspectives

Springer Reference

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With 67 Figures and 117 Tables

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Foreword

Substance use and abuse is widespread around the world. There are clear cultural differences between countries and sometimes even within the same country regarding the use and abuse of substances. Various cultural and social factors play an important role in defining and treating patterns of substance abuse. Reasons for substance use and abuse vary from genetic, social, and psychological. Depending upon the degree of abuse and recognition of the patterns of abuse, help may be sought from a number of sources. Cultures and societies dictate how resources are allocated and how people are encouraged to use certain pathways into care. Identifying the unmet needs and mental health gap in the field of substance use and abuse is the first crucial step.

This reference text – a significant output from the International Society of Addiction Medicine – meets the aims of the Society. These aims are eminently laudable as they recognize the role of physicians in treating and managing addictions. The key challenges remaining include policy differences across countries and how these must be addressed. Furthermore, training of all health professionals in recognizing physical and psychiatric problems associated with substance abuse is a must. Depending upon human and financial resources, perhaps a tiered approach may be indicated. Physicians in partnership with others have a significant role to play in a public mental health agenda. Substance abuse – varying from tobacco to drugs, prescribed or otherwise – is a major challenge in the field of public mental health. The editors have done a sterling job in bringing together over 250 authors from a rich global background to have shared their expertise and experiences. This volume provides an excellent introduction at an international level to epidemiology, biological, social, and psychological interventions and recognition of medical consequences and comorbidities. The editors deserve our congratulations on a job well done.

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The past decade has witnessed disturbing growth in the prevalence and diversity of substance use problems throughout the world. First considered a "US problem" and later a problem "of the Western world," substance abuse and addiction are now clearly world-wide problems producing dramatically greater loss of life, morbidity, and costs than virtually any other health condition.

Perhaps because addictions have been so prevalent and serious in the USA for the past 40 years, over 80 % of published clinical research on addiction to alcohol and other drugs of abuse has been done by the USA and other English-speaking investigators. But this body of work has at best only partially informed our understanding of how to prevent and treat addiction. This is because so many factors that contribute to susceptibility to initial substance use; transition from voluntary use to uncontrolled addiction; and to treatment entry, adherence, and effectiveness are determined as much by environmental, family, and interpersonal forces as they are by genetics and metabolism. These factors vary substantially across countries and cultures. Thus, world understanding about how to prevent, intervene early, and treat addiction will require far more diverse study.

In this context, the *ISAM Textbook of Addiction Treatment*, with its broad and diverse contributions representing 265 scientists and 30 countries, is a timely and welcome addition to worldwide understanding on how to intervene and treat addictions. In particular, the *Textbook* introduces a wide range of new perspectives on the development of substance use disorders and a number of previously unreported interventions to reduce the prevalence, severity, and associated harms from substance abuse and addiction.

To be sure this *Textbook* will not resolve decades-long controversies in optimal prevention, intervention, and treatment responses, there is still too little information and too many preexisting views to yet achieve consensus. But this *Textbook* signals something that has frankly been lacking in US-dominated research and treatment of addiction: a willingness to incorporate, evaluate, and include effective *new* approaches, methods, and tools. It is clear that no country, profession, or theory can claim adequate success in preventing or treating addiction to justify the all-too-common political, financial, and even scientific resistance to new methods.

If there is a need to reduce diversity, it is in our methods of diagnosing substance use disorders, in articulating common goals of treatment, and in adopting common measures and methods for evaluating treatment access, adherence, and effectiveness. These kinds of consensus standards should help this still-developing field of public and clinical health to identify and agree upon effective

new interventions. This is an obvious and needed role for the *International Society of Addiction Medicine* and should be a natural outgrowth of continued international collaboration and sharing of results through venues such as this *Textbook*.

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The initiative to write a textbook addressing the global aspects of addiction, whether prevalence, types, and methods of abuse or different management approaches, is unique and welcome. The chapters are comprehensive to deal with all psychosocial–biological aspects of addiction. Psychoactive substance use poses a significant threat to the health, social, and economic fabric of families, communities, and nations. The extent of worldwide psychoactive substance use is estimated at 2 billion alcohol users, 1.3 billion smokers, and 185 million drug users.

In an initial estimate of factors responsible for the global burden of disease, tobacco, alcohol, and illicit drugs contributed together 12.4 % of all deaths worldwide in the year 2000. Looking at the percentage of total years of life lost due to these substances, it has been estimated that they account for 8.9 %.

The level of economic development in countries also plays an important role. The burden from psychoactive substance use is higher in developed countries than especially in high-mortality developing countries. The sex ratio for the attributable deaths of psychoactive substance use varies from 80 % male for tobacco and illicit drug use to 90 % for alcohol. With regard to DALYs, it is between 77 % and 85 % for all substances. The largest proportion of DALYs is on males in developed countries, where psychoactive substance use accounts for 33.4 % of all DALYs (WHO Website).

WHO seeks to promote the concept of health for all through its strategy of reducing the incidence and prevalence of psychoactive substance use and providing the best available evidence on the management of substance-related problems. The achievement of this goal is designed to lead to reductions in the demand for psychoactive substances and to reduce the health and social problems associated with such use.

The debate that we are criminalizing cannabis while decriminalizing alcohol and tobacco in spite of their higher disease burden is controversial (Okasha 2008). The use of replacement therapy in addiction in developed countries may be unavailable in emerging countries. What are the alternatives? We have contradictory feedback from different countries. I believe this book will enlighten those working in the mental health of addiction in different developed, emerging, or developing countries to comprehend the complexity of the problem of addiction and the necessity to use flexible programs according to the norms, culture, and economy of the country.

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Preface: What Does an International Perspective Bring?

The International Society of Addiction Medicine (ISAM) was founded in Palm Springs in 1999. From the onset, the elements of its main mission were

- *Advancement of the knowledge of addiction as a treatable disease*
- *Recognition that physicians worldwide have a major role to play in the management of addiction*
- *Enhancement of the credibility of the physician's role*
- *Emphasis of the importance of educational activities*
- *Establishment of consensus documents and practice guidelines*

To implement this mission, the Society has organized an annual meeting ever since. This major gathering has also been supplemented on a few occasions with regional meetings. The Society also cosponsors the journal *Substance Abuse*. To pursue the mission, an International Certification in Addiction Medicine was created in 2005 and has been administered annually on a total of 15 occasions.

In seeking reference texts to create the examination questions for the Certification, it became evident that the three or four excellent multiauthored textbooks available in English all originated from the USA, with an occasional contribution from an author from another country. These books are heavily centered on data arising from an American context and culture. We decided that a textbook with a broader authorship representation was required as well as a search for data originating from across the world. Mindful of the fact that authors would potentially have different degrees of English proficiency, we divided the scope of our chapters into overview, focused, and sidebar chapters for case studies. International strategies to address substance abuse have traditionally favored control of the supply of drugs rather than reduction of the demand for their use. This textbook aims to describe the multifaceted options available for culturally sensitive strategies prioritizing demand reduction.

This international textbook is divided into 12 sections, resulting from the collaborative efforts over 3 years of some 265 contributors from 30 countries. These sections outline the components of an international perspective.

A broader understanding of epidemiology, etiology, and prevention

The prevalence of drug intake is determined not only by individual stress factors but also regional and larger-scale cultural patterns of drug consumption, social role models, as well as legal requirements and prohibitions.

A common sequence is for the onset of substance abuse to be largely influenced by cultural factors; environmental and social factors are important in the transition to hazardous consumption, while neurobiological and other risk factors become more salient in the transition to substance use disorder.

The genetic and epigenetic components of the heritability of addiction also point to cross-population differences in risk susceptibility across large samples. These considerations consequently inform the spectrum of applied prevention strategies.

An appreciation of the arduous search for a common language as well as means of detection and intervention

A historical review of the concept of substance use and its disorders illustrates differences in international perspectives and challenges in achieving a universal taxonomy. Currently, the recent aggregation of the concept of dependence with that of substance abuse in the latest DSM-5 is in contrast with the efforts of the ICD10 review to retain "hazardous use" as a separate entity. This new DSM-5 spectrum, largely based on questionnaire data, will require further clinical validation.

While there is consensus about the benefits of screening and brief intervention strategies, the selection of optimal screening instruments, laboratory detection methods, and brief intervention techniques is the subject of an international effort to assess cross-cultural validity as well as investigate cost-effective laboratory tests and intervention strategies to accommodate the world's range of financial and practice resources.

The global facets of drug abuse and the current and future of biological approaches

The differential availability of traditional drugs such as alcohol, tobacco, opioids, and cannabis along with newer drugs such as cocaine, amphetamines, hallucinogens, sedatives, and anabolic steroids is evident across the global stage and brings insights into the origins of abuse. Furthermore, our shrinking world is more and more subject to epidemics of new products sweeping from one continent to the next. The trend is for laboratory-manufactured chemicals to replace plant-derived drugs. The latest surge of crystal methamphetamine is now followed by the emergence of synthetic cannabinoids; the creation of these new drugs will unfortunately continue.

Advances in neurosciences have so far yielded about a dozen drug-specific medications, and access to this small number is further limited by conservative national policies, economic constraints, and lack of clinicians' expertise. The good news is that there is also mounting evidence of efficacy from a number of diverse complementary options such as acupuncture, biologics, transcranial magnetic stimulation, nutrients, phytomedicines, and mind-body treatments. The evidence for these approaches originates from around the globe, where some of these techniques derive from a long-standing acculturation.

Behavioral approaches and the balance of fidelity and adaptation

Globally, behavioral approaches are a major element of treatment. Over the last 50 years, these therapies have evolved from generic advice-giving and confrontational strategies to more sophisticated, evidence-based techniques aimed at improving retention in treatment and positive reinforcement of change. Behavioral approaches are either directed at the individual or at groups, couples, families, and communities.

Not all such approaches have been evaluated to the same extent, with the major effort directed at the investigation of Motivational Interviewing, Cognitive Behavioral Therapy, and Contingency Management.

Challenges in the international dissemination of these approaches include the significant effort required for the transfer of knowledge and skills as well as the need to balance the evidence-based principles and methods of the approach with the adaptation needed to incorporate new cultural contexts and values in a translated language. Like in the biological approaches, innovative techniques continue to be created and are at various stages of investigation.

Social therapies and their accessibility

Faced with the difficulties in abating, if not ending, the disease of addiction, a diverse group of socially grounded therapies have sprung worldwide. Approaches have included peer-led movements with no formal affiliation such as the 12-step programs which are spanning most of the globe. Other peer-led programs have evolved as institutions regulated by governments such as therapeutic communities. These approaches are not identical worldwide but have nevertheless many similarities. A major advantage of these approaches has been their cost-effectiveness rendering them accessible to a range of economic capabilities.

The second advantage has been their adaptability to social institutions as diverse as the workplace, the justice system, or the residential treatment programs. These approaches have gained widespread acceptance particularly in developing countries.

The diverse elements of a systems approach

A community treatment system requires a comprehensive network of different approaches, services, and participants. A public health perspective stresses connections among services. These services share concepts of different indications and rules for patient pathways through treatment phases following a stepped care model.

The network, in addition to formal therapeutic regimes, includes low-threshold approaches through outreach activities and harm reduction interventions. The resources and priorities will of course differ between developing and developed countries. A comprehensive network remains a work in progress with continuous adaptations. An overall drug policy document should reflect political support to provide adequate and sustainable resources.

A system must include continuous monitoring and evaluation. The education and training of staff must be informed by the results of the evaluation. Stakeholders are to be involved in the priority setting as well as ethical and legal considerations.

What constitutes a behavioral addiction?

Over the last 30 years, an increasing range of behaviors have been recognized as susceptible to develop from excessive engagement to a habitual or compulsive pattern. In addition to the investigation of common biological and psychological underpinnings, an international perspective highlights the difference between the required quasiuniversal use of a medium like the Internet and the susceptibility to develop an Internet addiction along sociocultural differences. The same applies to the meeting of basic needs such as food, sex, or exercise and their evolution into

compulsive behaviors. Leisure activities such as gambling and videogames may also follow the same pathway. Ever-increasing access to services, products, and credit may accelerate this course.

Other insights are arising from the study of behavioral addictions as windows into human nature without the effects of substances. A model of addiction is emerging, depending less on "harm-based" negative consequences which are subject to ever-changing cultural values and judgment calls and more on the presence of such concepts as craving, loss of control, impulsivity, compulsion, mood dysregulation, and/or cognitive distortions.

Differences in treatment seeking patterns, treatment approaches, and settings as well as goals of treatment are highlighted in an international comparative analysis.

The recognition of medical consequences and comorbidities

The principles of assessment and management of the medical consequences of drug use ought not to be different around the world, and yet morbidity and mortality rates of drug users vary markedly due to differences in the general health status of the population, access to health care, and rates of treatment uptake and dropout. An estimated one-third of the global population is living with one or more bacterial or viral infections. Nutrition is important, and nutritional disorders impact on recovery from other co-occurring illnesses. The availability and acceptability of simple preventive measures like the use of a condom significantly affect the rate of sexually transmitted infections. The medical consequences of drug use interact in each country with the general level of hygiene as well as availability of preventive and treatment resources. While the management of acute disorders is the main focus of health resources in developing countries, chronic disorders including chronic pain become the major concern in developed countries, and substance use plays an important role in the course of both these acute and chronic disorders.

The co-occurring care of substance use and psychiatric disorders and system change

While the recognition of medical comorbidities has not resulted in an overall health system change, a reorganization is occurring in the addiction and mental health fields. Since the 1950s, the recognition of the co-occurrence of substance use and psychiatric disorders and its impact on the delivery of services has evolved. In most developed countries, the addiction field struggled to establish its own system of delivery of care based on the need to treat otherwise unrecognized or marginalized individuals with addictive disorders. In the United States, NIDA and NIAAA as separate research institutes led the building of a scientific knowledge foundation for our field. Worldwide, various degrees of separation remained in existence with many countries maintaining the addiction services under the umbrella of mental health.

For the last 30 years, increased recognition of the high prevalence of individuals with co-occurring disorders has resulted in a replanning of the coordination between addiction and other mental health services and in some cases integration of both systems. Based on improved empirical evidence in both fields, this renewed coordination is leading to enhanced attention to the neurobiological interface as well as pharmacological and psychotherapeutic combined options. The redesign of

optimal systems of care as well as related workforce training is ongoing. Diagnostic-based approaches now integrate the treatment of substance use and other psychiatric disorders.

The dilemmas of special populations

The challenge of prioritizing special groups for further recognition is a daunting one, and there is no international consensus. Our own selection included women, addressing half of humanity as well as the elderly soon to become a quarter of humanity. The LGBT group provided an example of the impact of significant stigmatization. Much attention has been directed at the care of physicians and other health care providers as an example of evidenced excellent outcome when well-defined workplace strategies are in place. Our last two groups involved the "displaced" populations either through conflicts or disasters; internationally, these groups are in the millions!

Perhaps a common feature of these groups is a sense that their fit within the general system of care may not be optimal, and there is demonstrated evidence that some of their needs may be better met wholly or partly in distinct pathways of care.

Meeting the needs of our youth

Contrary to the previously listed groups, there is international consensus that the youth of the world deserve their own care. Much is to be gained by a focused system for young people who use drugs. They face the higher risk of initiating substance use. This initiation is determined by a multitude of risk factors in different developmental contexts, some of it originating from parental chronic substance use.

Adolescence is also a critical period where protective factors can also modify the pathways to substance use. The earlier the intervention during that period, the more chance there may be of a successful outcome including the prevention of chronicity and the reduction of the risk of suicide. Knowledge of the impact of both risk and protective factors can also optimize preventive strategies.

The engagement of a young person who is often vulnerable and even marginalized may require the involvement of multiple systems along with repeated assessments. Greater specificity in treatment choice that is developmentally appropriate such as CBT and MET along with family-based interventions have been demonstrated to provide the most consistent gains. Barriers to involvement must also be addressed such as stigma, safety, transportation, and family commitment.

Educating, training, and sustaining our workforce

The education, training, and sustenance of an appropriate workforce are critical to the survival of our field. A range of pioneering efforts is available. They are based on an increasingly consensual framework of identified competencies recognized by specialty associations as well as a number of universities through a master's degree.

Recognition of these competencies is facilitated through diverse pathways such as an American Board Examination, an International Certification (ISAM), and a number of diploma degrees. The knowledge base is accessible through a number of Open Access literature repositories or educational activities such as the Treatnet program. Fellowships in research training are available through NIDA, and a number of travel fellowships to conferences are offered.

Concerning the recognition of a specialty status, there is no "one size fits all" model. This journey must adapt to local educational and licensing requirements that govern the national practices of medicine.

Beyond training, the recruitment of an adequate workforce must take into consideration the provision of attractive career paths countering stigma as well as adequate remuneration and working conditions.

In conclusion, as no country has so far been able to eradicate the misuse of substances or control excessive behaviors, pooling the international experience is warranted. A global scanning of the options allows us to forecast potentially promising approaches. Considering the world experience, we are also reminded of the dictum "Absence of evidence may not necessarily mean evidence of absence." It may just be that the evidence has yet not been unearthed and our current investigations are still not sensitive enough.

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Section I

Basic Sciences and Clinical Foundations

Andreas Heinz and Nady el-Guebaly

Basic Sciences and Clinical Foundations: An Introduction

1

Andreas Heinz and Nady el-Guebaly

Abstract

We here introduce the section "Basic Scienes and Clinical Foundations". In this section we will adress the social, cultural, and regional as well as the neurobiological and genetic aspects of addiction. The foundational section of this international textbook on addiction treatment aims to provide an apt prologue to the topic. This section includes chapters on neurobiology, a thorough review of the neurotoxic and neuroadaptive consequences of chronic drug intake with a focus on alcohol. A chapter on genetics presents the heritability of addiction and its genetic and epigenetic components; another chapter presents the international epidemiological aspects of addiction with a focus on the findings of the Global Burden of Disease study. Another focus is on sociocultural dimensions, thus two chapters present roles of socio-environmental factors in diagnosis and treatment and their impact on the patient-clinician interpersonal dynamics as well as interaction with the family, intimate social networks, community at large, and policy makers. Moreover, we show cultural factors, i.e., the shared beliefs, norms, and patterns of behaviors. The social patterning of psychoactive drug use differs as to whether it is medicinal, regular, intermittent, or addictive. Finally, two other chapters focus on the prevention applications of the

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components discussed with review of the international experience. In conclusion, this foundational section provides an informative basic science review of current knowledge. As this is the first section of this textbook the aim is to demonstrate the basic sciences and clinical foundations; and to reflect the commonalties and differences of broad global and international perspectives.

Drug use and dependence is one of the leading causes of disability and suffering particularly in adolescence and younger adults (Gore et al. 2011). Addictive disorders also contribute to a substantial percentage of interpersonal violence, partly due to the direct effect of drugs of abuse such as alcohol (Heinz et al. 2011) and partly due to social consequences of illicit drug abuse (Macleod et al. 2004; Nutt et al. 2007; Toumbourou et al. 2007). In this section, we will discuss the social, cultural, and regional as well as the neurobiological and genetic aspects of addiction. The appreciation of this term has evolved. In 1976, Griffith Edwards suggested to focus on key aspects of drug dependence, namely, tolerance to drug effects developing with its chronic (ab)use and withdrawal symptoms appearing when chronic drug use is suddenly intermittent (Edwards and Gross 1976). He suggested replacing the term "addiction," as more likely to stigmatize patients because it points to strong drug urges and the allegedly impaired ability to control such desires. Edwards instead proposed to focus on the "somatic" aspects of the addictive disorders, most notably tolerance and withdrawal. However, tolerance also develops to nonaddictive drugs such as β-blockers, which are used as antihypertensive medication, and withdrawal symptoms emerging as a sign of impaired cerebral homoeostasis can appear when β-blocker consumption is suddenly stopped (Karachalios et al. 2005). Therefore, current textbooks of addictive disorders often tend to emphasize the craving for the drug of abuse and the impaired ability to control the consumption of this drug in spite of its adverse effects as key aspects of addictive disorders (American Psychiatric Association and DSM-5 Task Force 2013).

Craving, loss of control, and consumption despite negative consequences have often been labeled as the "psychological" symptoms of an addictive disorder, while tolerance development and withdrawal symptoms have been called "somatic" signs of the disease; however, in our view, this distinction between psychological and somatic symptoms of addictive disorders should no longer be supported, as both withdrawal symptoms and craving for the drug of abuse have cerebral correlates. Tolerance development is associated with neuroadaptations within affected neurotransmitter systems, and withdrawal symptoms result from an imbalance between central excitatory and inhibitory neurotransmitters, causing an overshoot of autonomic nervous system responses (Hughes 2009). Craving in turn might be attributable to dysfunctions of motivational systems including dopaminergic neurotransmission in the ventral striatum (Heinz 2002; Everitt et al. 2008). Furthermore, current theories of addictive behavior emphasize a gradual shift from goal-directed, reward-seeking behavior towards automatic drug intake, a concept that has previously been promoted by Tiffany and Carter (1998) with respect to nicotine dependence and that has currently gained a lot of behavioral as well as neurobiological support

in animal experiments and human studies focusing on chronic drug intakes (Everitt and Robbins 2005). These considerations show that far from being limited to either the psychological or somatic domain, all key aspects of addictive disorders such as tolerance development, withdrawal symptoms, drug craving, and impaired control of drug use are associated with central nervous system correlates and neuroadaptations.

Modern theories of psychiatric disorders integrate subjectively reported symptoms such as craving or urges to consume a drug with behavioral variables such as acute or habitual drug intake and their respective neurobiological correlates (e.g., activation of the ventral or dorsal striatum and the respectively associated frontocortical-striatal-thalamic loops (Chen et al. 2011; Goldstein and Volkow 2011; Peters et al. 2011)). Moreover, neurobiological research has often pointed to the intimate interaction between social stress effects and the development and maintenance of drug addiction (Heinz et al. 2011; Hinckers et al. 2006). For example, exposure to developmentally early social isolation stress in nonhuman primates promotes excessive alcohol intake, and the degree to which such social effects impact on the neurobiological correlates of addiction is modulated by genetic variability (Barr et al. 2003; Fahlke et al. 2000; Heinz et al. 2011; Higley et al. 1991).

Beyond individual social stress factors, regional and large-scale cultural patterns of drug consumption, legal requirements, and prohibitions as well as complex social role models all contribute to the prevalence of drug intake (el-Guebaly et al. 2002; Rehm et al. 2003). Also, modern cosmopolitan societies need to consider the effects of different explanatory models of addictive disorders. For example, we and others have observed that it may not suffice to translate information material to prevent the development of addictive disorders because the concept, the terms, and the general understanding of addictive behavior can vary substantially between persons and cultures and misunderstandings can only be avoided if local and linguistic concepts of "normal" and "harmful" drug use are known (Penka et al. 2008; Vardar et al. 2012).

Our textbook addresses all the above named aspects of addiction. The foundational section of this international textbook on addiction treatment aims to provide an apt prologue to the topic. It consequently includes articles on the burden of disease, the cultural as well as genetic aspects of addictive disorders, and the neurobiology of addiction and also on the resulting strategies for prevention and treatment of drug use and dependence.

The first chapter on neurobiology by Sebold and Garbusow is a thorough review of the neurotoxic and neuroadaptive consequences of chronic drug intake with a focus on alcohol (▶ Chap. 2, "Neurobiology of Addiction"). Dispositional factors such as the level of response to alcohol and early social deprivation are reviewed. The stimulatory and sedative effects of acute alcohol consumption are then outlined, followed by a discussion of the animal and human studies underpinning the concept of a reward system and the important differentiation between the experiences of "liking" and "wanting." The chapter concludes with an analysis of the consequences of chronic alcohol consumption as well as insights for new pharmacological treatment.

The second chapter on genetics by Dr. Rutter presents a complementary perspective to the first one (▶ Chap. 3, "The Genetics of Addiction: A Global Problem with Global Opportunities"). An introduction reviews the heritability of addiction and its genetic and epigenetic components, including the startling finding that our genetic individuality resides in 0.4 % (about 12 million) of the nucleotides in the DNA sequence. The examples provided are derived from cross-population analyses of nicotine dependence, thus providing an insightful window into our second "legal" drug. The chapter concludes with a futuristic perspective on the implications of genetics for treatment and the emergence of pharmacogenetics.

The third chapter by Dr. Rehm et al. presents the international epidemiological aspects of addiction with a focus on the findings of the Global Burden of Disease study (▶ Chap. 4, "Burden of Disease: The Epidemiological Aspects of Addiction"). Regional differences are compared. A sequence emerges whereby the onset of substance abuse is largely influenced by cultural factors; environmental and social factors are important in the transition to hazardous consumption, while neurobiological and other risk factors become more salient in the transition to substance use disorder. A striking example of the relative importance of these factors is presented in a case vignette about the rapid changing patterns of use in Georgia since gaining its independence and the relaxation of state control, by Drs. Kirtadze and Otiashvili. The public health impact of intravenous and polysubstance drug use and a resulting epidemic of infectious diseases are leading to a contemplation of much needed drug policy reforms.

An international textbook ought to pay particular attention to sociocultural dimensions. Consequently, the next two chapters present two complementary perspectives on this topic. Dr. Westermeyer presents a theoretical analysis of the roles of socio-environmental factors in diagnosis and treatment and their significant impact on the patient-clinician interpersonal dynamics as well as interaction with the family, intimate social networks, community at large, and policy makers. A list of recommendations for positive governmental actions is included.

Dr. Room in the next chapter focuses on the cultural factors, i.e., the shared beliefs, norms, and patterns of behaviors. The social patterning of psychoactive drug use differs as to whether it is medicinal, regular, intermittent, or addictive. The handling of alcohol and drug problems often changes over time, for example, from a judicial to a health problem. The chapter concludes with Alcoholics Anonymous as an example of core practices worldwide but also local cultural adaptations. A description of Japanese support groups is provided in Section V on "▶ Social Therapies and Treatment Settings: An Introduction".

The last two chapters focus on the prevention applications of the components previously discussed with review of the international experience. Drs. Burkhart and Simon from the European Monitoring Centre for Drugs and Drug Addiction first describe a logical frame for prevention and assessment of its effectiveness. The basics of several prevention strategies are then described including mass media campaigns and environmental prevention. The benefits and limitations of different targets of the preventative efforts range from the population at large to vulnerable groups to family-based prevention and indicated prevention for individuals.

The second part by the same authors discusses the important regional and cultural aspects of prevention. Societal values influence student and adolescent behaviors as well as parenting practices. Again, an international perspective is presented as to recent developments and trends in preventative measures. Examples of the previously described strategies in different regions of the world and their relative acceptance are described along with resulting lessons about successful transfer and adaptation of the experience between continents and countries.

In conclusion, we hope this foundational section provides an informative basic science review of current knowledge. Due to the different scientific backgrounds involved, several "Glossaries of Terms" are included. The first section of this textbook aims to reflect the commonalties and differences of broad global and international perspectives as salient determinants of management strategies.

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Neurobiology of Addiction

2

Miriam Sebold, Maria Garbusow, Christian A. Müller, Katrin Charlet, and Andreas Heinz

Contents

Abstract

Chronic drug intake (including alcohol) has profound neurotoxic and neuroadaptive consequences on neurotransmitter systems and brain circuitries that are strongly involved in learning and memory. Neuroadaptive alterations within these systems can contribute to addiction development and maintenance. Current brain-imaging studies identified neural correlates of behavioral processes that play a key role in addiction, such as cue-induced craving or automatic action tendencies. Such neurobiological findings reflect neuroadaptations to

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chronic drug intake, to further environmental as well as genetic factors and serve as dispositional factors for the maintenance of addictive behavior patterns. In this chapter, we describe neurobiological theories of addiction development and maintenance with a focus on motivational alterations and their neurobiological correlates as revealed by current neuroimaging studies in alcohol dependence. We discuss findings that assess alterations in reward anticipation and processing and their respective effects on learning mechanisms that are known to be implied in alcohol dependence. A better understanding of neural processes directly associated with the development and maintenance of addiction can help to improve prevention programs as well as therapeutic and specifically pharmacological interventions in the treatment of addicted patients.

Abbreviations

5-HTT	Serotonin transporter
ACC	Anterior cingulate cortex
ADH	Alcohol dehydrogenase
ALDH	Aldehyde dehydrogenase
CNS	Central nervous system
CS	Conditioned stimulus
dlPFC	Dorsolateral prefrontal cortex
DRD2	D2 receptors
EEG	Electroencephalogram
fMRI	Functional magnetic resonance imaging
GABA	Gamma-aminobutyric acid
GHB Acid	Gamma-hydroxybutyric acid
HPA	Hypothalamic-pituitary-adrenal
ICD-10	International classification of diseases 10th revision
MID task	Monetary incentive delay task
mPFC	Medial prefrontal cortex
MRI	Magnetic resonance imaging
ms	Milliseconds
NAcc	Nucleus accumbens
NMDA	N-methyl-D-aspartate
OFC	Orbitofrontal cortex
PET	Positron emission tomography
PFC	Prefrontal cortex
SSRIs	Selective serotonergic reuptake inhibitors
US	Unconditioned stimulus
VTA	Ventral tegmental area
WHO	World Health Organization

2.1 Introduction

The dependence syndrome is characterized by cognitive and physiological phenomena after repeated substance intake including continuous drug intake despite the knowledge of its negative consequences in order to reduce physiological and psychological withdrawal symptoms. Further symptoms are a high priority given to drug use, the development of tolerance towards the specific drug effects, a strong desire to take the drug, and the inability to stop or control the drug intake or the amount of the consumed drug (International Classification of Diseases, 10th revision (ICD-10); Dilling et al. 2011). According to *The Global status report on alcohol and health* (2011a), the World Health Organization (WHO) described a prevalence of 4 % of alcohol use disorders worldwide with more than 2.5 million people dying annually due to the consequences of hazardous alcohol intake, which as a causal factor exceeds global death rates caused by HIV/AIDS or tuberculosis (WHO 2011a). Regarding nicotine dependence as another common substance use disorder, there are currently more than one billion tobacco users (WHO 2011b), and about five million deaths are caused by direct tobacco smoking (WHO 2012), pointing to the serious physiological harm of tobacco consumption. However, both alcohol and nicotine dependence as common use disorders of legal and socially accepted substances do not only cause severe somatic effects, but also have profound social, economic, and psychological impact on the dependent individuals and society. Since up to 85 % of the patients suffering from alcohol dependence and up to 80 % of smokers relapse after detoxification, respectively smoking cessation (Boothby and Doering 2005; Zhou et al. 2009), strong effort has been made to investigate the underlying pathophysiological mechanisms in the development and maintenance of substance use disorders and to identify their neurobiological substrates. By using brain imaging techniques, neural correlates of processes have been identified that are assumed to be involved in relapse, such as craving or cue-induced, automatic drug intake (Beck et al. 2012; Tiffany 1990). The goal of such studies is to shed light on the neurobiology of drug addiction as well as to provide new options for specific behavioral and pharmacological interventions. For instance, neuroimaging studies that predict relapses in detoxified patients based on neural activation pattern have potential clinical implications: Programs treating addiction might use information about neural correlates of relapse prediction in order to assess patients who have a high risk of relapse to higher levels of care. In this chapter, we will illustrate neurobiological theories of addiction development and maintenance. We will focus on the neurobiology of alcohol dependence and describe excitatory and sedative effects and their neurobiological substrates of acute alcohol intake. We will describe neuroadaptive effects of excessive chronic alcohol consumption and present neuroimaging studies that discovered alterations in neurotransmitter systems and their impact on functional neural activity in alcohol dependence.

2.2 Neurobiological Factors for the Development and Maintenance of Alcohol Dependence

2.2.1 Dispositional Factors for the Development of Alcohol Dependence

Several risk factors for the development of alcohol dependence have been reported in the literature including the influence of genes and environment (Ehlers and Gizer 2013; Zimmermann et al. 2007). We will focus on key mechanisms identified in animal experiments and human studies.

2.2.1.1 Level of Response to Alcohol

One dispositional factor that has been discussed in the literature is the individual response to alcohol: individuals with a low level of response to alcohol, i.e., who consume and need higher amounts of alcohol to experience any stimulating effect and who experience sedative effects only after higher doses of alcohol, tend to use alcohol excessively and seem therefore to be at a higher risk of developing alcohol dependence (Paulus et al. 2012; Schuckit 2000; Schuckit and Smith 2000, 2006). Thus, low sensitivity towards the effects of ethanol predicts future heavy alcohol consumption (Schuckit et al. 2009b) and alcohol-related problems (Schuckit et al. 2009a). This endophenotype represents a genetically influenced trait with a heritability rate of 40–60 % and can be observed more often in subjects with a positive versus negative family history of alcoholism (Paulus et al. 2012), pointing further to a close gene-environment association. Concerning the neurobiological correlates of this trait, human studies using functional magnetic resonance imaging (fMRI) reported that the neural processing of cognitive demands (Paulus et al. 2006; Schuckit et al. 2012; Tapert et al. 2004b; Trim et al. 2010) and emotional stimuli (Paulus et al. 2012) is affected by the individual level of response to alcohol: increased brain activations mostly in the frontal gyrus and cingulate gyrus during trials with emotional faces or demanding – high working memory load – trials (required for usual performance) were associated with a low level of response to alcohol in healthy adolescents (Tapert et al. 2004b) and in young adults (Paulus et al. 2006, 2012; Schuckit et al. 2012; Trim et al. 2010). This may reflect the need of compensatory brain activation for adequate processing of contextual information which has also been observed in alcohol-dependent patients compared to healthy volunteers (Pfefferbaum et al. 2001; Vollstädt-Klein et al. 2010a). Further, alcohol challenge studies reported that in contrast to subjects with a high level response to alcohol, moderate doses of alcohol attenuate this "default" hyperactivity in individuals with low sensitivity to alcohol without affecting their performance (Paulus et al. 2006, 2012; Schuckit et al. 2012; Trim et al. 2010), assuming that after drinking those individuals adapt a more efficient processing, i.e., less effort in suppressing irrelevant information (Paulus et al. 2006; Trim et al. 2010).

Also concerning the genetic influence on alcohol sensitivity, candidate genes encoding the enzymes alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH), which are involved in the metabolism of alcohol, also interact with the

amount of alcohol consumption and thus the risk of developing alcohol dependence (Birley et al. 2009; Frank et al. 2011; Hurley and Edenberg 2012). When alcohol is metabolized, acetaldehyde is produced as the first intermediate product by ADH (Spanagel 2009). Acetaldehyde is assumed to be responsible for some short- and middle-term consequences of excessive alcohol intake such as the feeling of "hangovers" due to its own harmful effects to the body. Primarily in East Asian population, protective ADH variations occur resulting in rapid accumulation of acetaldehyde, which triggers an unpleased "flush" reaction including erythema (redness of the skin) of parts or, in some cases, the entire body and therefore often results in less alcohol consumption (Hurley and Edenberg 2012). Thus, variations in the ADH genes influence alcohol sensitivity, i.e., the acute effects of alcohol consumption (Birley et al. 2009; Chen et al. 2009; Hurley and Edenberg 2012; Whitfield 1994). Altogether, these studies suggest that less negative and aversive effects of acute alcohol consumption are associated with more intake and a higher risk to develop alcohol dependence (Heinz et al. 2001; Schuckit and Smith 1996).

2.2.1.2 Early Social Deprivation

People suffering from psychiatric disorders are often limited in their social interactions; on the other hand, environmental factors (such as social deprivation early in life, isolation or abandonment) can increase the risk to develop psychiatric disorders including drug dependence (Heinz et al. 2011; Meyer-Lindenberg and Tost 2012; Pruessner et al. 2004). Experiencing social stress activates effector systems such as the hypothalamic-pituitary-adrenal (HPA) axis and can sensitize the mesolimbic dopamine system (Heinz 2002; Meyer-Lindenberg and Tost 2012; Pruessner et al. 2004). For example, in nonhuman primates, Nader et al. (2006) observed in a study using positron emission tomography (PET) that low social status was associated with higher (potentially stress-induced) dopaminergic concentrations in the extracellular space (reflected a radioligand binding to dopaminergic D2 receptors) and with increased cocaine intake.

Furthermore, it was demonstrated that in primates, early social deprivation, which induces stress, leads to serotonergic dysfunction, which was associated with high levels of aggression, a low level of response to acute alcohol intoxication and higher alcohol intake (Heinz et al. 1998a). Young primates who were separated from their mother in early infancy displayed a lower level of serotonin turnover, a higher availability of serotonin transporters (5-HTT) and lower level of response to alcohol. In this study, the 5-HTT increase appears to have been a consequence of stress-induced reduction of the turnover of serotonin (Heinz et al. 2000). A high level of 5-HTT availability may also be due to genetic variation (Lesch et al. 1996) and may thus affect alcohol intake: In line with this assumption, Hinckers et al. (2006) observed that subjects with a genetic disposition for a high availability of 5-HTT displayed low alcohol sensitivity which was correlated with higher alcohol consumption in adolescents.

Moreover, rodent studies showed that social isolation during a critical period of adolescence enhances the glutamatergic N-methyl-D-aspartate (NMDA) receptors

in the ventral tegmental area (VTA) (Whitaker et al. 2013). The VTA is the center of origin of striatal dopaminergic projections and is thus significantly involved in reward-based learning as well as in the development of dependent behavior. In these socially isolated rats, Whitaker et al. (2013) observed an increased learning rate for drug-associated stimuli, which was more resistant to extinction, suggesting that NMDA receptor plasticity is one mechanism though which the vulnerability of drug dependence is adjusted during a critical period in adolescence (Whitaker et al. 2013).

2.2.2 Effects of Acute Alcohol Consumption

It is assumed that moderate acute alcohol intake is linked to consequences such as stress reduction and relaxation via the sedating effect of alcohol (Zimmermann et al. 2007), physiological excitation (improved performance on motor, cognitive, and information-processing tests), a decrease of negative mood states (like anxiety and depression), increased talkativeness, as well as feelings of euphoria and increased sociability (Ekman et al. 1963; Gilman et al. 2008; Williams 1966). The ability of alcohol to reinforce its acute intake increases the probability of repeated alcohol consumption and thus is a key condition for developing excessive intake (Heinz et al. 2012).

Since ethanol passes the blood-brain barrier quickly after alcohol consumption, several neurotransmitter systems are affected by acute alcohol consumption (Charlet et al. 2013; Lindenmeyer 2001): Here, enhancing and stimulating effects as well as inhibitory effects of ethanol are mediated by the time course of the respective activation of dopaminergic, serontoninergic, opioidergic, gamma-aminobutyric acid (GABA)ergic, and glutamatergic neurotransmission, modulating the individual vulnerability to develop alcohol dependence.

2.2.2.1 Stimulatory Effects of Acute Alcohol Consumption

Ethanol acts as a stimulant via its excitatory effects on the central nervous system (CNS), which can be perceived as rewarding. Conscious affective experiences of alcohol consumption have, e.g., been documented by Williams (1966), who reported a decreased negative affective status (less anxiety and less depression) after the intake of low levels of ethanol in healthy volunteers. Moreover, positive effects on the behavioral level like increased talkativeness, elation, happiness, euphoria, relaxation, stress reduction, and increased sociability and anxiolytic effects have been reported (Duka et al. 1998; Ekman et al. 1963; Gilman et al. 2008). Gilman et al. (2008) measured the rewarding and anxiolytic effects of alcohol using fMRI in social drinkers receiving ethanol injection. The authors observed that alcohol activated the dopaminergic striatal reward system which correlated with higher self-ratings of intoxication, regardless of presenting threatening or nonthreatening emotional stimuli to the participants, (Gilman et al. 2008). The authors suggested that this anxiolytic effect of alcohol may affect the ability of decision-making after alcohol consumption, thus subjects may underestimate

dangerous situations. The experience of strong stimulating effects of ethanol on the one hand and low sedative or aversive effects on the other hand was associated with a higher risk for increased alcohol consumption and the development of alcohol-related problems (Holdstock et al. 2000; Newlin and Thomson 1990).

Serotonergic neurotransmission is assumed to be involved in mediating the acute effects of alcohol as well as modulating aggressive behavior and negative mood states (Bushman and Cooper 1990; Heinz et al. 2001) and in a low response to alcohol. Serotonin hereby, e.g., interacts with dopaminergic neurotransmission, which plays a key role in integrating motivational and motor functions (Heinz et al. 2001, 2003; Knutson et al. 1998; Robbins et al. 1989). Serotonergic neurotransmission seems to play a key role in the development rather than the maintenance of alcohol dependence: in a study by LeMarquand et al. (1994), serotonergic uptake inhibitor like citalopram and fluoxetine decreased alcohol intake in moderate social drinkers. However, studies of selective serotonergic reuptake inhibitors (SSRIs) do not clearly support their effectiveness in alcohol treatment (Garbutt et al. 1999; Kiefer and Mann 2005). This may be due to the fact that anxiety and depression, which correlate with 5-HT dysfunction after detoxification (Heinz et al. 1998b), do not predict relapse during the first month of abstinence. Rather, anxious subjects tend to be more cautious and to avoid harm, and depression only predicts relapse if persisting for a long time after detoxification (Heinz et al. 2001).

2.2.2.2 Sedative Effects of Acute Alcohol Consumption

With increasing doses of alcohol consumption, sedative effects of ethanol occur (Martin et al. 1993). These inhibitory alcohol effects could be associated with negative mood states and the subjective experience of a hangover (Nagoshi and Wilson 1989). In comparison to the stimulatory effects that reflect the rewarding aspects of alcohol consumption and reinforce alcohol intake, sedative and unpleasant effects may thus tend to decrease alcohol use (Ray et al. 2009; Schuckit and Smith 1996). Here, high amounts of alcohol inhibit/interfere with glutamatergic neurotransmission (Carlson and Lydic 1976; Cohen et al. 1997). It has been hypothesized that sedative effects induced by ethanol reflect a generally lower activity of the cerebral cortex (Hendler et al. 2013). For example, a PET study by De Wit et al. (1990) revealed that glucose metabolism after acute consumption of ethanol is decreased in the whole brain, particularly at higher doses. Furthermore, brain regions associated to specific behavioral impairments induced by alcohol intake have been identified. For example, impaired motor coordination, which was associated with reduced functioning of the cerebellum (Hanchar et al. 2005); PFC impairment was associated with impairments in executive cognitive functions, including planning, verbal fluency, memory and complex motor control in healthy control receiving different doses of alcohol (Peterson et al. 1990), as well as cognitive flexibility, information processing speed, and planning and problem solving in patients suffering from alcohol dependence (Zorko et al. 2004).

Consumption of high doses of ethanol appears to be particularly relevant in adolescence, because this life span is a critical period of cortical development which can be disrupted by alcohol intake (Crews et al. 2007). Interestingly, animal

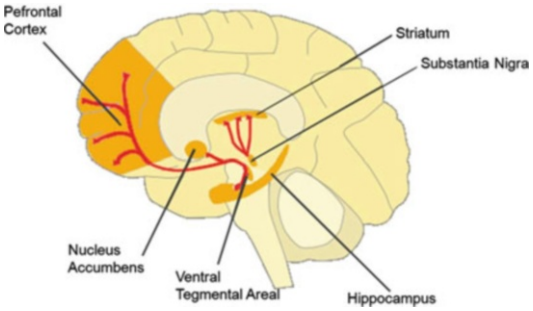

Fig. 2.1 The dopaminergic mesocorticolimbic circuit: the VTA, ventral striatum, including the nucleus accumbens (NAcc), dorsal striatum, the amygdala, frontal and limbic circuits. Key regions of the so-called neural "reward system"

studies show that adolescence is a period with a decreased sensitivity to the sedative effects of acute alcohol consumption, with adolescents showing substantially less acute alcohol sensitivity (Silveri and Spear 1998). Monti et al. (2005) observed that adolescent as well as alcohol-preferring rats show low sedative effects of alcohol, comparable to humans at risk for developing an alcohol dependence (Schuckit and Smith 1996). Critically, this may entice adolescents to binge drink, although, they are more vulnerable than adults to neurotoxicity induced by ethanol (Crews et al. 2000; Monti et al. 2005). Crews et al. (2000) described binge drinking-induced brain damages in adolescent rats in frontal and temporal cortical regions, while adult rats showed no binge drinking-induced alterations in these areas. In line with this, De Bellis et al. (2005) observed in a human study using magnetic resonance imaging (MRI) a smaller PFC in subjects with an adolescent-onset-alcohol use disorder. Here, a smaller PFC correlated with a higher number of drinks per drinking episode and a higher number of drinks per maximum drinking episode (De Bellis et al. 2005).

2.2.3 Addiction and the Reward System

2.2.3.1 Disentangling "Liking" from "Wanting"

Key regions of the so-called brain "reward system" are innervated by dopaminergic neurons ascending from the ventral tegmental area (VTA) and substantia nigra via the ventral (including the nucleus accumbens (NAcc)), and the dorsal striatum, and the amygdala to frontal and limbic circuits (Ikemoto 2007) (see Fig. 2.1). All drugs of abuse have in common that their intake leads to increased dopaminergic neurotransmission in the ventral striatum and the NAcc (Di Chiara and Imperato 1988). As natural or primary (like food, sex, or sleep) and secondary reinforcers (like money) also elicit dopaminergic release, it was initially suggested that dopamine mediates reward and causes hedonic feelings (Wise 1982). Thus, the mesocorticolimbic circuit has often been termed as the neural "reward system." However, this assumption was challenged by studies that demonstrated symptoms of apathy instead of anhedonia in subjects who received pharmacological blockage of dopaminergic neurotransmission such as neuroleptics (Acquas et al. 1989;

Heinz 2002). It was therefore suggested that dopamine mediates motivational behavior towards reward instead of consummatory pleasure – therefore functions as a neural correlate of "wanting" instead of "liking" (Berridge 2009). It is generally assumed that "liking" (experience of pleasure) on the neurobiological level is associated, e.g., with the opioidergic neurotransmitter system, and on a neuroanatomic level with activity within the NAcc and the ventral pallidum (Le Merrer et al. 2009). Evidence for a functional role of the opioidergic system in mediating hedonic effects of reward comes from human studies and animal experiments: Animal studies using mu receptor knockout mice showed decreased food intake (Papaleo et al. 2007) and insensitivity toward the hedonic effects of morphine (Matthes et al. 1996). In accordance with this, nalmefene – a μ-opiate receptor antagonist decreases subjective pleasantness of palatable foods in humans (Yeomans and Wright 1991). Besides food reward, the opioid system further seems to mediate hedonic and affective value of drug reward, including alcohol consumption. Thus, it was shown that a genetic variation of the μ-opiate receptors is associated with more intense response to alcohol (Ehlers et al. 2008) and with alcohol craving (Heinz et al. 2005a). Moreover, naltrexone, a μ-opiate receptor antagonist that is administered for craving reduction in addiction treatment is assumed to block the hedonic effect of alcohol, thus reducing relapse rates and alcohol intake in alcohol-dependent patients. Thus, the opioidergic system is assumed to serve as a neural correlate of "liking" and may therefore mediate positive emotions, such as pleasure, hedonism, or reward when drugs are consumed. Dopamine, on the other hand, appears to play a key role in mediating "wanting," thus signaling behavioral significance and triggering motivation. Evidence for this comes from studies that demonstrated increased dopaminergic neurotransmission when reward occurs unexpectedly or when it is greater than expected, thus signaling salience and consequently motivates the individual to strive toward the reward (Schultz 1998).

2.2.3.2 Dopamine in Mediating Learning Effects

Dopaminergic firing increases when reward-predicting cues appear, thus mediating reward anticipation and reinforcement learning. Primarily, Schultz (1998) demonstrated a shift in phasic dopaminergic activity from the received reward to the reward-predicting cue, as soon as subjects have learned the contingency between the reward and the stimulus. However, learning via dopaminergic transmission is also established when experiences other than reward were paired with a previous neutral cue: For example, phasic dips in dopaminergic activity were observed when an outcome is worse than expected (Schultz 1998; see Fig. 2.2). Indeed, there is accumulating evidence that intact dopaminergic transmission is essential for extinction learning, for instance, for the deletion of conditioned responses to stimuli that are no longer associated with reward (Quirk and Mueller 2008). Drugs of abuse elicit dopaminergic neurotransmission to a greater extent and to a more immediate effect (Goldstein 2001) than natural, biologically essential (primary) rewards (Heinz et al. 2012). Moreover, compared to natural reinforcers, the effect of drugs on dopaminergic release does not seem to habituate (Di Chiara and Bassareo 2007),

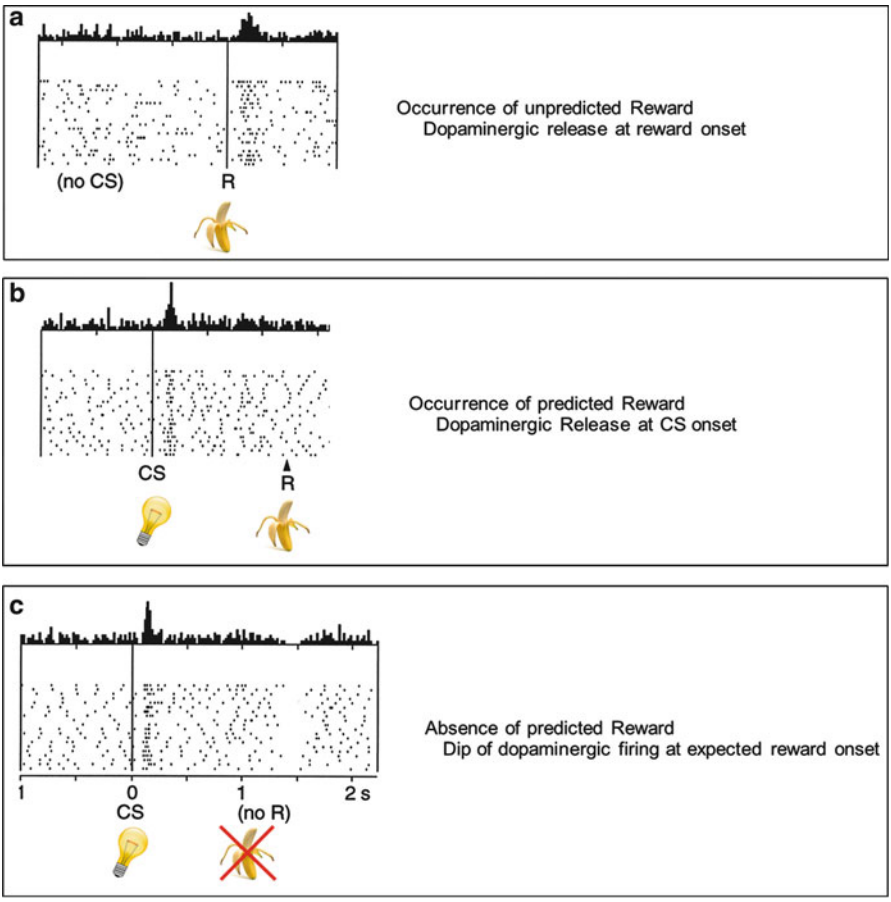

Fig. 2.2 (**a**) Burst of dopaminergic firing in occurrence of an unpredicted reward (R) at reward onset (positive prediction error). (**b**) After pavlovian conditioning: burst of dopaminergic firing not at reward but at conditioned stimulus (CS) onset. (**c**) No reward: Dip of dopaminergic firing at expected reward onset (negative prediction error) (Adapted from Schultz (1998))

because the pharmacological effect of the drug itself causes a persistent dopaminergic release in the striatum (Wise and Rompre 1989). Furthermore, in animals (Paulson and Robinson 1995), repeated administration of drugs fosters augmented dopamine release. This phenomenon – commonly termed as sensitization – was also confirmed to some degree in humans (Boileau et al. 2006). Thus, repeated administration of addictive drugs might cause a hypersensitive dopaminergic system. Moreover, it has been suggested that in addiction, dopamine is released by formerly neutral cues that have predicted drug intake previously (Heinz 2002). Several animal studies demonstrated that in addiction drug-associated stimuli activate dopamine release in the medial prefrontal cortex and the ventral striatum (Bassareo et al. 2007; Dayas et al. 2007; Di Chiara 2002; Shalev et al. 2002). These findings have been extended to

humans, as it was demonstrated that the expectation of amphetamine effects also elicits an increased dopaminergic transmission (Boileau et al. 2007). Crucially, these dopaminergic releases might signal increased salience of specific drug-associated stimuli and thus potentially capture and hold the individual's attention (Robinson and Berridge 1993). In alcohol dependence, external stimuli of visual or olfactory modality, such as the sight of an alcohol bottle in the supermarket or the smell of it in a pub might serve as such predicting cues.

2.2.3.3 Incentive Salience Theory of Addiction

The adaptation of phasic dopaminergic signals over the course of learning appears to reflect the assignment of value to cues (Flagel et al. 2011). Thus, in addiction it has been proposed that environmental stimuli, which have repeatedly been paired with drugs, acquire incentive salience as a result of pavlovian learning (Robinson and Berridge 2008). More precisely, it is assumed that these drug-associated stimuli can become "motivational magnets" as they attract attention and guide approach behavior (Berridge 2009). Indeed, when intravenous cocaine administration is reliably and repeatedly paired with an external cue (illuminated lever), rats approach the illuminated lever more likely and with increasing rapidity, so the cue now became a conditioned stimulus representing the cocaine reward (Uslaner et al. 2006). Moreover, an increase of alcohol consumption has been observed in the presence of stimuli that have formerly been presented during alcohol intake (Corbit and Janak 2007; Glasner et al. 2005). The attribution of incentive salience to drug-associated stimuli is thought to be closely linked to the observation that addicted subjects show significant reactions to drug-related stimuli even when no drug is administered, a phenomenon commonly referred to as cue-reactivity (Carter and Tiffany 1999).

Cue-induced activity in addiction has been demonstrated to exist on a variety of physiological levels including changes in heart rate, sweat gland activity, skin temperature, and functional brain activity (Carter and Tiffany 1999). These physiological changes are assumed to reflect automatic conditioned responses that are not under conscious control. Studies using stimuli that are presented below conscious threshold demonstrated these "automatic" physiological responses to drug-related cues. In a neuroimaging study conducted by Childress et al. (2008), cocaine-addicted patients displayed increased limbic activation when confronted with cocaine-related pictures for only 33 ms. Further cue-induced neural reactions towards drug-related context have been assessed with different neuroimaging techniques: heavy but not light drinkers displayed increased neurophysiological activity in frontal regions in the electroencephalogram (EEG) when watching alcohol-related cues for only 500 ms (Herrmann et al. 2001). Furthermore, Petit et al. (2012) demonstrated in a recent study that when confronted with alcohol cues, heavy social drinkers displayed poorer inhibitory ability in a visual Go/No-Go task: here a response is claimed in the Go condition and should be inhibited in the No-Go condition announced by a specific signal, respectively. Another study assessed neural activation patterns using fMRI during the presentation of pictures of alcoholic drinks and neutral cues to heavy and light social drinkers and observed

a heightened alcohol cue-induced neural activation of the dorsal striatum in heavy social drinkers, while light social drinkers showed increased activation in the ventral striatum and prefrontal "cortical control" regions (Vollstädt-Klein et al. 2010a). As the authors suggested, this may indicate resilient neural patterns preventing the light social drinkers from the development of alcohol dependence (Vollstädt-Klein et al. 2010b). In accordance with this, in a recent study conducted by Beck et al. (2012), patients prospectively remaining abstinent displayed intact ventral striatal activation when confronted with alcohol cues, while patients who prospectively relapsed did not.

Increased physiological cue-reactivity was also reported in relation to consciously experienced cue-reactivity, as indicated by self-reported measurements that assess increased craving or the desire for a particular substance of abuse (Schulze and Jones 2000; Vollstädt-Klein et al. 2010a). Interestingly, a study investigating the response of light, heavy social drinkers and alcohol-dependent patients to alcohol-related cues reported different effects on craving associated with the content of the alcohol cues used: while pictures displaying solely alcoholic beverages induced more craving in the patient group, complex social scenes with alcoholic beverages were more likely to elicit craving in the group of heavy social drinkers, referring to a shift of the rewarding aspects and positive expectations of drinking in a social context in social drinkers towards the habitual motivated aspects of alcohol itself in alcohol-dependent patients (Lee et al. 2006). However, it has been demonstrated that subjective and physiological cue-reactivity can be dissociated, as physiological cue-induced responses in addiction resemble responses elicited by affectively positive stimuli, albeit subjects deny conscious feelings of pleasure (Heinz et al. 2003; Mucha et al. 2000).

2.2.3.4 Habitual Drug Seeking

Whereas the incentive salience theory suggests that in addiction, drug-associated cues become motivationally highly attractive and therefore "wanted," Tiffany's theory of addiction suggests that drug consumption reflects a habitual responding that is controlled by automatically initiated action schemata (Tiffany 1990). Thus, in addiction, drug-associated stimuli might not elicit a positive affective or motivational state that results in drug-seeking behavior. Rather, according to Tiffany's theory in addiction, drug consumption happens to occur in a habitual fashion, as it might be automatically initiated mostly independent of actual reinforcer contingencies and current reward values (Stephens et al. 2010; Tiffany 1990). Theoretical arguments for habits as a key role in drug addiction were based on the observation that drug consumption in addiction seems to be fast and efficient, initiated and completed without intention, difficult to impede in the presence of triggering stimuli, effortless, and conducted in the absence of awareness (Tiffany 1990). Further evidence for habitual drug consumption comes from clinical observations of addicted patients: many relapses happen to occur without any preceding urges to consume drugs or conscious craving (Tiffany 1990). According to their "transition to habit" theory, Everitt and Robbins (2005) suggested that addiction reflects the

endpoint of a series of transitions: from initial drug intake that causes hedonic feelings (liking) to a stage when substance use becomes habitual (wanting) and ultimately to a loss of control that is characterized by compulsive drug seeking and intake. Habitual drug consumption is assumed to be disentangled from anticipatory drug effects. Evidence for this comes from animal studies: rats that have learned a specific response in order to self-administer drugs continue to perform this response even when drug delivery is suppressed (Katner et al. 1999; Katner and Weiss 1999). Thus in addiction, action selection may no longer be guided by outcome expectancy, but rather be driven by external sensory information that elicits pavlovian-conditioned responses. The standard test of habitual action selection is the demonstration that sensory-specific devaluation or revaluation of rewards has no immediate effect on choice behavior. In the devaluation design the value of a specific reward is decreased, for instance, by associating it with sickness, whereas in the revaluation design, the value of the reward is increased, for instance, by determining to experience the reward in a state of deprivation. Crucially, neither devaluation nor revaluation of a stimulus alters choice behavior on that stimulus, when action selection is habitual. This has been supported by studies demonstrating that unlimited access to alcohol fosters ethanol consumption in rats, which is insensitive to quinine, which has a bitter taste and is thus not rewarding (Hopf et al. 2010; Wolffgramm and Heyne 1995). Crucially, it has been demonstrated that responding for ethanol becomes insensitive to devaluation at a stage when responding for food reward is still sensitive to devaluation, indicating that the shift from goal to stimulus-directed consumption is more rapid for alcohol than for natural rewards (Dickinson et al. 2002).

On the neural level "wanting" might be mediated by the ventral striatum and the state of habitual intake by the dorsal striatum. Thus the development of an addiction might be mediated by a transformation from goal-directed to stimulus-driven, automatic behavior, which is assumed to be accompanied by a shift of ventral to dorsal striatal activity. Animal studies seem to confirm this contention: once substance use becomes habitual, drug-associated stimuli foster release of dopamine in the dorsal striatum (Balleine et al. 2007; Corbit et al. 2012; Ito et al. 2002; Wong et al. 2006). However the translation of observations in animals excessively trained to perform lever presses for food or drugs, which finally habitize, to human behavior, which can be consciously reflected and verbalized, is controversial. Existing studies in humans have demonstrated that smoking cessation in nicotine-dependent subjects increases motivation for tobacco smoke (Madden and Bickel 1999; Perkins et al. 1996), indicating goal-directed responses in nicotine dependence. However, as these tests were not conducted in extinction, the effect of deprivation might have been mediated by the experience of an increased reward value in the deprivation state rather than the altered reward value of the expectancy (Stephens et al. 2010).

Also compulsions and obsessions as in obsessive compulsive disorder (OCD) do hardly resemble habitual intake (Schoofs and Heinz 2013). Therefore, the role of habitual vs. goal-directed drug intake in humans in addiction remains to be explored.

2.2.4 Consequences of Chronic Alcohol Consumption

2.2.4.1 Cue-Reactivity

Physiological and subjectively experienced cue-reactivity has been suggested to play an important role in addiction maintenance and relapse. More precisely, in addiction it is assumed that drug-associated stimuli signal upcoming reward and thus prompt drug-seeking behavior (Robinson and Berridge 1993). This evidence has been generated from a number of studies using fMRI in order to investigate neural correlates of cue-reactivity. These studies have shown that substance-dependent subjects display increased activation of several core regions of the mesolimbic pathway, when confronted with drug-associated stimuli. This finding has been reported in various substance dependencies, including heroin (Yang et al. 2009; Zijlstra et al. 2009), cocaine (Volkow et al. 2006), alcohol (Beck et al. 2012; Grüsser et al. 2004; Schacht et al. 2013; Tapert et al. 2004b; Wrase et al. 2007), cannabis (Filbey et al. 2009), and nicotine dependence (Bühler et al. 2010; David et al. 2005). Although these studies suggest substantial overlap between neural structures implicated in cue-reactivity, the identified brain structures considerably vary between studies, depending on the experimental design of the study (duration of stimulus presentation, block design vs. event-related design), cue-modality (visual, olfactory, gustatory), and state of the subjects (detoxified patients or actively drinking, treatment seeking vs. no treatment seeking patients) (Heinz et al. 2010; Yalachkov et al. 2012). Brain regions which have reliably been identified in different cue-reactivity fMRI studies include the anterior cingulate cortex (ACC), the medial prefrontal cortex (mPFC), the ventral and dorsal striatum and the orbitofrontal cortex (OFC), the dorsolateral prefrontal cortex (dlPFC), and the amygdala (Charlet et al. 2013, see Table 2.1). Several neuroimaging studies also reported correlations between cue-induced hyperactivity in the mesolimbic circuit and self-reports of craving in substance-dependent patients, suggesting that cue-related neural activation of reward-associated brain regions may be associated with the motivation to consume drugs and therefore with prospective relapse. In alcohol dependence, a positive correlation between craving and cue-induced neural activity was found in the subcallosal gyrus (Tapert et al. 2004a), the ventral striatum, the orbitofrontal cortex, and the anterior cingulate cortex (Myrick et al. 2004). As the assessment of craving is limited by the fact that it relies on individuals' ability to accurately rate and report their own desire for the substance, some studies add more objective relapse indicators, such as days of abstinence in a given observation period following brain imaging assessment. Here, cue-induced activity in the ventral putamen/striatum (Braus et al. 2001) and the medial prefrontal cortex (Grüsser et al. 2004) predicted relapse in detoxified alcohol-dependent patients within a follow-up period of 3 months. A recent study by Beck et al. (2012) observed that functional connectivity patterns differ between prospective relapsers and abstainers from alcohol: while subsequent relapsers displayed increased neural activation in the medial prefrontal cortex during the presentation of alcohol-associated versus neutral stimuli, subsequent abstainers activated midbrain regions, such as the ventral tegmental area including the subthalamic nucleus and showed increased functional connectivity between the

Table 2.1 Core regions activated by alcohol-related stimuli in imaging studies using cue-reactivity paradigms

Brain structure	Function	Study	Study design of cue reactivity paradigm
Anterior cingulate cortex (ACC)	Performance monitoring and error detection, encoding of motivational salient stimuli	Tapert et al. (2003)	Alcohol-related vs. nonalcohol pictures
		Grüsser et al. (2004)	Alcohol-related vs. neutral pictures
		Heinz et al. (2004)	Alcohol-related vs. neutral pictures
		Myrick et al. (2004), Myrick et al. (2008)	Priming dose of alcohol; alcohol-related vs. nonalcohol-related pictures
		Tapert et al. (2004a)	Alcohol-related vs. neutral words
		Vollstädt-Klein et al. (2011)	Alcohol-related vs. neutral pictures
Medial prefrontal cortex (mPFC)	Memory and decision making	Grüsser et al. (2004)	Alcohol-related vs. neutral pictures
		Myrick et al. (2008)	Priming dose of alcohol; alcohol-related vs. nonalcohol-related pictures
		Beck et al. (2012)	Alcohol-related vs. neutral pictures
Orbitofrontal cortex (OFC)	Evaluation of reward	Wrase et al. (2002)	Alcohol-related vs. abstract neutral pictures
		Myrick et al. (2004)	Priming dose of alcohol, alcohol-related vs. nonalcohol-related pictures
Dorsolateral prefrontal cortex (dlPFC)	Executive behavioral control	George et al. (2001)	Priming dose of alcohol, alcohol-related vs. nonalcohol-related pictures
Amygdala	Specification of emotional salience	Schneider et al. (2001)	Olfactory cues associated with ethanol vs. neutral odor
Dorsal striatum	Consolidation of stimulus-reaction patterns and habit formation	Modell and Mountz (1995)	Multiple sips of alcohol-related vs. multiple sips of water
		Grüsser et al. (2004)	Alcohol-related vs. neutral pictures
		Vollstädt-Klein et al. (2010b)	Alcohol-related (complex scenes) vs. neutral pictures

(*continued*)

Table 2.1 (continued)

Brain structure	Function	Study	Study design of cue reactivity paradigm
Ventral striatum	Motivational aspects of salient stimuli and association with motor responses	Braus et al. (2001)	Alcohol-related vs. neutral pictures
		Wrase et al. (2002)	Alcohol-related vs. neutral pictures
		Wrase et al. (2007)	Alcohol-related vs. neutral pictures
		Myrick et al. (2008)	Priming dose of alcohol, Alcohol-related vs. nonalcohol-related pictures
		Vollstädt-Klein et al. (2010b)	Alcohol-related (complex scenes) vs. neutral pictures
		(Mann et al. 2011)	Alcohol-related vs. neutral pictures
		Ihssen et al. (2011)	Alcohol-related vs. neutral pictures

midbrain, amygdala, and the orbitofrontal cortex. This observation may suggest that (preserved) integrity of a circuit that is implicated in the processing of aversive aspects and the danger of alcohol intake may represent a resilience factor against relapse (Beck et al. 2012).

2.2.4.2 Neuroadaptive Dopaminergic Changes

Chronic alcohol intake has been demonstrated to be associated with profound neuro-adaptive and neurotoxic effects on dopaminergic, GABAergic, serotonergic, and glutamatergic neurotransmission. For instance, alcohol-dependent patients display low levels of dopamine synthesis and release as well as an decreased availability of D2 receptors (DRD2) in the ventral striatum (Heinz et al. 2004, 2005b; Volkow et al. 1996). A positive correlation between the reduction of DRD2 and lifetime alcohol intake (Heinz et al. 1996) suggests that these neuroadaptive alterations might be due to excessive alcohol consumption rather than genetically prerequisites. The extent to which DRD2 and dopamine synthesis are decreased was correlated with self-reported craving for alcohol, which predicted relapse (Heinz et al. 2005b). In accordance with the observation that up to 70 % of all placebo-treated alcohol-dependent patients relapsed within the first 12 weeks after detoxification (Boothby and Doering 2005), it has been demonstrated that the described alterations in the dopaminergic neurotransmission recover within the first days to weeks after detoxification (Heinz et al. 2005b). Thus, it has been suggested that in early phases of abstinence, the described neuroadaptive changes of dopaminergic neurotransmission cause the individual to strive for particularly strong activators of the downregulated dopaminergic system such as drugs or drug-associated stimuli, which are effective enough to elicit a substantial dopaminergic

response in spite of the generally reduced neurotransmission. This is in line with the finding that the degree of striatal downregulation of DRD2 in alcohol dependence is associated with the extent of drug-cue-induced activation in the medial prefrontal cortex and the anterior cingulate and with the severity of alcohol craving (Heinz et al. 2004). It has been suggested that the bias towards high dopaminergic stimulatory drugs can bias choices against weaker primary and secondary reinforcers such as food, money, or social interactions. A current study of Kienast et al. (2013), who combined PET and fMRI, further suggests a failure of dopamine-modulated emotion processing of aversive stimuli in alcohol-dependent patients. Here, no association was found between dopamine synthesis in the amygdala and functional activation in the amygdala and ACC elicited by aversive emotional stimuli in recently detoxified alcohol-dependent patients, while such correlations were observed in healthy volunteers (Kienast et al. 2008). Furthermore, the patients displayed impaired functional connectivity between the amygdala and the ACC while viewing the aversive cues, which may contribute to increased trait anxiety due to malfunctional corticolimbic neuromodulation. Negative mood states, such as high anxiety, can lead to an increased relapse risk especially in late abstinence (Kienast et al. 2013).

Dopaminergic dysfunction may primarily interfere with learning of new conditional stimuli and contexts that predict nondrug reward. Indeed a study demonstrated impairments in learning from nondrug-related rewards in alcohol dependence (Park et al. 2010), which correlated with craving for (well-learned non-explicit) alcohol intake. The shift of natural reward processing to preferential drug-related reward processing has been metaphorically described as a "hijacking of the reward system," which was substantiated by several studies using a Monetary Incentive Delay task (MID, Knutson et al. 2001). For example, it was shown that alcohol-dependent subjects compared to healthy controls displayed a decrease in ventral striatum activity during expectation of monetary gains but an increased activation in the same region when confronted with drug cues (Beck et al. 2009; Wrase et al. 2007). Activity in the ventral striatum elicited by drug cues was correlated with self-reports of craving (Wrase et al. 2007). These findings are in line with other studies suggesting an essential role for the ventral striatum in relapse prediction. For instance, the degree of ventral striatal activity elicited by drug-associated stimuli presentation was associated with time until relapse (Braus et al. 2001) and the amount of prospectively consumed alcohol (Grüsser et al. 2004), suggesting that the ventral striatum plays a role not only in the acquisition but also in the maintenance of alcohol dependence. In accordance with the assumption of a hijacked reward system, it has been suggested that strong neural responses to rewarding, nondrug-related stimuli might serve as a potential protective brain mechanisms against relapse. Indeed, it was demonstrated that increased ventral striatal responses to affectively positive connoted pictures were related to more subsequent abstinent days and less prospective alcohol intake (Heinz et al. 2007). Furthermore, Charlet et al. (2013) observed heightened neural responses to emotionally negative facial stimuli in the ACC, which also predicted better treatment outcome (days of abstinence and days of binge drinking) in

a 6-month follow-up period in detoxified alcohol-dependent patients. Since the anterior cingulate cortex is involved in the adequate attribution of people's intentions as well as in error monitoring and emotion control, the integrity of this specific brain area might thus represent one resilience factor protecting patients from relapse despite stressful social situations (Charlet et al. 2013).

2.2.4.3 Neuroanatomical Alterations

Alcohol as a neurotoxic substance causes widespread neural alterations when chronically consumed: up to 70 % of alcohol-dependent patients show alcohol-associated brain atrophy, i.e., tissue loss of grey and white matter, ventricular enlargement, and sulci widening (Carlen et al. 1978; Oscar-Berman and Marinkovic 2007; Schroth et al. 1988). Morphometric studies investigating brain volume changes in alcohol dependence found that this atrophy affects frontal, temporal, and parieto-occipital regions but also the hippocampus, the corpora mamillaria, as well as the cerebellum, with the most marked atrophic changes within the white and grey matter of the frontal lobe (Kril et al. 1997; Moselhy et al. 2001). In particular, volume deficits of frontal and parieto-occipital regions appear to be clinically relevant, since these changes were reported to be predictive of an earlier return to any alcohol use and the risk of relapse (Beck et al. 2012; Rando et al. 2011). These atrophic changes might lead to impairments of working memory and executive functioning, thus possibly reducing long-term action planning and inhibition of short-term reward-directed behavior (e.g., alcohol intake) (D'Esposito et al. 1995; Watanabe 1996). However, the precise pathophysiological mechanism of alcohol-associated brain atrophy is not fully understood; possibly, a hyperglutamatergic state during alcohol withdrawal leads to a calcium influx via activation of glutamatergic NMDA receptors and thereby initiates cytotoxic cascades (Tsai et al. 1995). Furthermore, alcohol withdrawal was reported to activate the HPA axis, resulting in elevated cortisol concentrations (Heinz et al. 2003). Cortisol concentrations in turn were associated with reduced 5-HTT availability in the brain stem, which also contributed to increased severity of depression in early abstinence (Heinz et al. 2003). Interestingly, these neuropathological changes seem to be partially reversible, because regenerations of brain volume during short-term alcohol abstinence were described in alcohol-dependent patients (Agartz et al. 2003; Bendszus et al. 2001).

2.2.4.4 Alcohol Tolerance and Withdrawal

Chronic substance use results in different neuroadaptive changes in the brain, leading to tolerance towards the acute effects of the substance and causing withdrawal symptoms when substance use is suddenly stopped. This neuroadaptation seems to be essential for the maintenance of homeostasis between excitatory and inhibitory functions in the brain and counteracts the (mostly inhibitory) acute effects of the drug of abuse (Koob and Le Moal 1997). As a consequence of these alterations, a reduction or cessation of substance use may lead to a severe disturbance of homeostasis, which can clinically manifest as psychovegetative withdrawal symptoms or epileptic seizures. Both development of tolerance and

withdrawal symptoms seem to be related to drug activation of GABAergic as well as inhibition of glutamatergic neurotransmission (Krystal et al. 2006; Tsai et al. 1995). GABA represents the main inhibitory neurotransmitter in the human brain and is involved in rapid information processing in cortical and subcortical areas. While acute alcohol consumption induces activation of inhibitory GABA-A receptors, leading to sedation after intake of large amounts of ethanol, chronic alcohol consumption seems to result in an increased tolerance for acute alcohol effects due to a systematic downregulation of GABA-A receptors. Long-lasting GABA-A receptor changes have been found in alcohol-dependent patients after several weeks of alcohol abstinence and even may persist long during further abstinence (Abi-Dargham et al. 1998). Regarding psychovegetative withdrawal symptoms, neuroadaptive changes within the glutamatergic system appear to result from chronic alcohol-induced antagonism of glutamatergic NMDA receptors. Indeed, a compensatory upregulation of glutamatergic NMDA receptors as a consequence of chronic alcohol intake has been observed (Ward et al. 2009). In case of reduction or cessation of alcohol consumption, the excitatory neurotransmitter glutamate then can activate an elevated number of NMDA receptors (Glue and Nutt 1990). This process can cause dysbalances between inhibitory and excitatory functioning with a predominance of excitation, which may result in epileptic seizures and disinhibition of noradrenergic neurons at the locus coeruleus, resulting in, e.g., vegetative withdrawal symptoms (Engberg and Hajos 1992).

2.2.5 Pharmaco-fMRI: New Insights of Pharmacological Treatment

Albeit treatment of drug-associated harm with drug substitution has been proven to be a very successful option in opiate addiction (Mattick et al. 2009), in alcohol addiction, treatment with substitutive psychoactive compounds (such as γ- Hydroxybutyric Acid, GHB) is prohibited in many countries, due to limited responder rates in GHB therapy (Maremmani et al. 2011). Instead, in many European countries, drugs potentially counteracting alcohol-associated neuroadaptations such as naltrexone or acamprosate are temporarily applied for relapse prevention. Even though Cochrane Reviews have demonstrated significant effectiveness of both pharmacological treatments (Relative Risk reduction of naltrexone (0.83) and acamprosate (0.86) compared to no medication) (Rösner et al. 2010a, b), the exact mechanisms by which acamprosate and naltrexone decrease alcohol ingestion and relapse rates in alcohol-dependent patients are yet to be explored. The application of neuroimaging techniques in pharmacologically treated alcohol-dependent patients is useful in predicting which medication helps to prevent relapse. For example, elevated levels of μ-opioid receptors have been observed in the ventral striatum of some detoxified alcohol-dependent patients (Heinz et al. 2005a) and are targeted by naltrexone, which blocks μ-opioid receptors.

A combination of fMRI and pharmacological treatment (Pharmaco-fMRI) allows to investigate how and where a specific pharmacological drug acts in the central nervous system. For example, a study conducted by Myrick et al. (2008)

demonstrated that naltrexone treatment produces significant reduction of cue-induced activity in the ventral striatum in alcohol-dependent subjects (Myrick et al. 2008). Notably, these changes in neural activity were additionally related to decreases in cue-induced craving, indicating a close link between pharmacological effects of naltrexone, striatal activation, and pharmacological craving modulation. Cue-elicited reduction in ventral striatal activation in detoxified alcohol-dependent patients under naltrexone has also been demonstrated by (Mann et al. 2011). Schacht et al. (2013) further suggested that the reduction of cue-induced activation in the OFC and the ventral striatum under naltrexone depends on genetic variations of the μ-opioid receptor gene and dopamine transponder gene, indicating that polymorphic variations in both genes should be considered in studies investigating the effect of naltrexone on reward processing. Further studies were conducted in order to assess the effectiveness of acamprosate. Acamprosate is assumed to reduce neuronal hyperexcitability, which may be responsible for acute alcohol withdrawal on the level of both excitatory glutamate and inhibitory GABA neurotransmitter pathways (Courtyn et al. 2001). In a study by Langosch et al. (2012), acamprosate treatment resulted in a significant reduction of cue-induced activity in the striatum and in the posterior cingulate in alcohol-dependent patients. However, this effect might not be solely due to the pharmacological treatment, as placebo treatment had a comparable effect on neural cue-induced activity. In fact, all patients from the study by Langosch received psychotherapy, indicating that this non-pharmacological treatment might have reduced neural cue-reactivity.

Besides naltrexone and acamprosate, alternative pharmacological treatments have been suggested to reduce craving and relapse rates in alcohol-dependent patients. One example for a new pharmacological treatment is baclofen, a GABA-B receptor agonist, which has raised attention since case reports and first clinical studies suggested its effectiveness in the treatment of alcohol-dependent patients (Addolorato et al. 2007; Ameisen 2005). A recent pharmaco-fMRI study has demonstrated that a single dose of baclofen diminishes resting state activity in limbic structures in nicotine-dependent patients (Franklin et al. 2012); baclofen application had previously significantly reduced the number of cigarettes smoked per day in nicotine-dependent subjects (Franklin et al. 2009). The authors of these studies hypothesized that baclofen might diminish the "limbic" substrate that is hyperresponsive to drugs and drug cues (Franklin et al. 2012).

2.3 Conclusion

Altogether neurochemical effects of acute alcohol intake are perceived as rewarding and therefore reinforce drug intake via pavlovian conditioning. These learning mechanisms appear to underlie a shift from occasional alcohol consumption to habitual intake (Heinz et al. 2009). Neuroadaptive alterations (particularly within the so-called reward system) are related to craving and increased processing of alcohol cues (Heinz et al. 2004). Thus, neurobiological

consequences of excessive alcohol intake are in accordance with the clinical observation (Tiffany 1990) that many alcohol-dependent patients find it particularly difficult to abstain from habitual consumption patterns and relapse after detoxification, despite high individual motivation to remain abstinent. Neuroimaging studies help to gain a better understanding of the neurobiological correlates of craving and motivation for alcohol intake, which can help to develop criteria for selective use of anti-craving medication. Furthermore, longitudinal and multimodal imaging studies might help to identify predispositional neurobiological markers for a high relapse risk and thus to offer patients their required higher intensity of treatment.

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Glossary of Terms

Action-outcome/Goal-directed Learning Instrumental actions that are acquired through response-outcome associations. Goal-directed actions are performed with the intention of obtaining the goal. Goal-directed actions are sensitive to devaluation/revaluation.

Devaluation A psychological design for the assessment of stimulus-triggered (habitual) responding. Animals are trained to perform two responses, one for each of two different rewards. One reward is then devalued by associating it with bad taste (via quinine), sickness (lithium chloride), or satiety (via pre-feeding). When given the opportunity to perform the instrumental responses again in extinction, the responses for the devalued reward should be selectively diminished, in case actions are controlled by outcome expectancy. Instead, when actions are stimulus-driven (thus habitual), actions for the devalued reward should not be altered.

Incentive A stimulus that promotes approach to a reward as a result of predictive associations with this reward. Incentives serve as motivational devices as they facilitate and energize behavior that has been associated with the reward. Incentives may acquire activational properties, which amplify the incentive properties of other incentive stimuli that occur concurrently, but are not necessarily related to the reward.

Liking Emotional affective value of reward that has hedonic impact and causes feelings of pleasure. In addiction research, self-reported measure of hedonia has been used as a proxy for liking.

Pavlovian conditioning (Classical conditioning) Associative learning, in which the conditioned stimulus (CS), comes to signal the occurrence of a second stimulus, the unconditioned stimulus (US), which elicits conditioned responses.

Reinforcer A stimulus that increases the probability of a desired response. In contrast to incentives, reinforcers elicit responding on the basis of their contingency with actions (instrumental conditioning).

Revaluation A psychological design for the assessment of stimulus-triggered (habitual) responding. The procedure is the same as in the devaluation procedure, except that the value of the (e.g., food) reward is increased, for example, by food deprivation of the animal. When actions are controlled by outcome expectancy, the selection of the revalued stimuli should be selectively increased. However, when actions are stimulus-driven (thus habitual), selection of the revalued reward should not be altered.

Reward A class of unconditioned motivational stimuli, which elicit pleasure and hedonic feelings that can act as positive reinforcers.

Sensitization A phenomenon that describes progressive amplification of responses after repeated administrations of a specific stimulus. Repeated administration of drugs may cause an enhancement of a directly elicited drug effect, i.e., sensitization. In animals, locomotor activity often functions as a measure for sensitization.

Stimulus-Response/Habitual Learning Instrumental responses that are acquired through the association of actions with stimuli. Habitual actions thus reflect the execution of stimulus-response associations. Habitual actions are enabled by particular stimulus configurations and thus insensitive to devaluation/revaluation. Habitual behavior comprises features of automaticity such as speed, autonomy, lack of control, and absence of conscious awareness.

Wanting Motivational value of reward that has decision utility. In addiction research, craving for the positive effects of drugs have been used as a proxy for wanting.

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The Genetics of Addiction: A Global Problem with Global Opportunities

3

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Contents

Abstract

Drug addiction is a chronic, relapsing brain disease characterized by compulsive drug seeking, craving, loss of self-control, and impaired decision making (National Institute on Drug Abuse NIDA – Drugs, brains, and behavior: the science of addiction. National Institutes of Health, U.S. Department of Health and Human Services, Washington, DC, 2010). Drug addiction persists in spite of many harmful physical and social consequences and cuts across geography, class, ethnicity, occupation, age, gender, and history. The science of genetics offers one approach to understanding individual differences in a complex disease like addiction. Genes provide a scaffold for normal development, for learning, and for pathophysiology. But genes do not act in isolation of other processes and genes alone do not cause addiction. Genes act within the environments of the cell, of the body, and of the world beyond the individual. Indeed, new

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discoveries in epigenetics demonstrate the reality by which environmental factors and exposures can regulate the activity of the gene. Addiction results from the interactive effects among multiple genes, acting in multiple environments and across multiple stages of development. This review, while focused on recent discoveries in genetics, argues that the global problem of addiction is best viewed through a prism that reflects the combined influences of genes, environment, development, and culture.

3.1 Introduction

The United Nations Office on Drugs and Crime (UNODC) serves as a warehouse for statistics about drug abuse. It reports that illicit drug users are found in every country, and drug abuse is among the top 20 risk factors associated with adverse health outcomes. On a global scale, the abuse of drugs is staggering: In 2012, out of a worldwide population estimated to be about 4.5 billion people aged 15–64 years, as many as 300 million used illicit drugs at least once in the past 12 months, 38 million were problem drug users, and 16 million were injection drug users, a primary vector for transmission of HIV and other infections (World Drug Report 2012).

To control the use of drugs, societies around the world employ a variety of approaches, from prohibition to criminalization, from "zero tolerance" to legalization. Marijuana is a good illustration of changing attitudes and differing approaches across the globe. As of this writing, the status within the United States, for example, is that 22 states and the District of Columbia allow the use of marijuana for medical purposes, while two states have recently (2012) legalized personal use. Coincidently, the 2012 Monitoring the Future Survey showed that regular marijuana use is on the rise in 8th, 10th, and 12th graders, with 6.5 % of 12 graders reporting daily/nearly daily use (Johnston et al. 2013). The survey also reports an increasing perception that marijuana is not harmful. Whether these laws and attitudes will promote addiction to marijuana or increase other negative consequences of abuse remains to be seen, but there is reason for concern. We know, for example, that the risk of addiction nearly doubles for those who start using in their teenage years, and it increases as well among daily users. Furthermore, the legalization of marijuana for recreational uses might spur competition among growers who could produce varying potencies across marijuana strains, leading to the possibility of higher addiction rates, as well as increased incidence of psychotic symptoms that are likely to appear in genetically vulnerable initiators (Tosato et al. 2013). There is an experiment of sorts in progress in the United States, and the full consequences of these approaches are unknown.

Alcohol and tobacco are the most widely used drugs globally and together account for high rates of mortality and morbidity. Alcohol dependence causes about 2.5 million deaths/year by exacerbating a variety of diseases in addition to alcoholism, including epilepsy, heart disease, cirrhosis, and cancer. The largest

killer, however, is smoking tobacco with nicotine as the major constituent responsible for addiction among smokers (Rehm et al. 2006; Mokdad et al. 2004; Henningfield et al. 1985), accounting for about 6 million deaths/year largely by causing cancer, heart disease, stroke, and respiratory disease. In the United States, approximately 435,000 deaths are attributed to tobacco, 85,000 deaths to alcohol, and about 17,000 due to illicit drug use, totaling about 537,000 US deaths per year due to addiction (Mokdad et al. 2004). The economic burden of drug abuse approaches 2 % of gross domestic product in some countries (World Drug Report 2012).

For some historical perspective on the number of deaths associated with drug abuse, consider that 20 million people died in the 4 years of World War I, some five million deaths per year. Similarly, World War II was fought over the course of 6 years, with a death toll of about 60 million, some 10 million per year. Tobacco, alcohol, and illicit drug use together contribute to an annual death toll of about 8.75 million, a figure that has been relatively constant over the last decade. With no end in sight, the global problem of addiction is clear. Given time, drug use and addiction will yoke the young, drain the health of the user, distort global economics, and penetrate political landscapes. Building the armament of biological knowledge is a critical piece in helping those affected.

3.2 Genetics of Addiction

3.2.1 Is Addiction Heritable?

We frequently observe that addiction runs in families. In addition to their genetic makeup, family members also tend to share environments as well as exposure to various environmental risk factors. Moreover, individuals may be affected differently by exposure to the same environment in ways that contribute to risk for disease. Fortunately, addiction is not an inevitable outcome of drug use. In fact, most people who initiate substance use recreationally do not become addicted. However, approximately 10 % of recreational users do become abusers, resulting from a cascade of brain changes that undermine the person's self-control and ability to resist intense impulses to take drugs (Leshner 1997; Kasanetz et al. 2010). Thus, a major challenge is to understand why some individuals are vulnerable to addiction whereas others are less so.

Genetics, the study of patterns of inheritance of given traits as they are passed down from parent to offspring, has made significant contributions to our understanding of addiction at both the population level and the molecular level. For decades, twin, adoption, and population studies from around the globe have demonstrated that the offspring of parents addicted to drugs are at increased risk of becoming addicted themselves (Dick 2011). Further studies using inbred strains of rodents or induced mutations in mice confirm the heritability of addiction. Of course, just as not everyone who takes drugs becomes addicted, not everyone born to drug-addicted

parents becomes addicted. Heritability studies agree that the proportion of phenotypic variance (i.e., addiction) attributable to genetic factors is in the range of 40–60 %, which leaves a similar proportion attributable to environmental factors.

It bears repeating that complex phenotypes like addiction are the result of complex interactions among genes and environments. Understanding the role of environmental influences on addiction can help home in on the genes that may be missed by genetic studies that ignore those factors (Hamza et al. 2011). Leveraging cultural patterns with appropriate study designs could be powerful for uncovering genetic risk and furthering our ability to educate, inform, prevent, and treat addiction. In the sections that follow, five key areas of addiction genetics are highlighted: phenotype; genetics and epigenetics; gene by environment interactions and prevention; neurobiology; and treatment and pharmacogenomics. Addressing these areas is critical for building the scientific foundation to tackle the global problems of addiction.

3.2.2 The Phenotype

To identify valid, meaningful genetic and environmental predictors of addiction, it is essential to define the phenotype of interest with as much precision as possible (Rice et al. 2001). Drug addiction is a conglomeration of various factors – compulsive drug seeking, craving, loss of self-control, and impaired decision making (National Institute on Drug Abuse – NIDA 2010). Ultimately, the successful identification and utility of specific genes, their biological pathways, and other etiological processes hinge on precise phenotypic definitions. An understanding of how such phenotypes are influenced and molded by environmental factors, developmental course, and other individual characteristics is a necessity.

Drug addiction is dynamic and characterized by cyclical patterns of harmful drug use, withdrawal, and relapse. It is further complicated by the involvement of multiple substances as well as cognitive, emotional, and social disruption in addition to the observable behavior patterns. Are these multiple disruptions merely consequences of drug abuse or do they suggest an underlying vulnerability as well? It has been hypothesized, for example (Palmgreen et al. 2007), that drug abuse is a consequence of sensation-seeking, impaired decision making, or weak executive control, all of which are functions of the frontal lobes of the brain, which in turn are gene regulated.

An important consideration in genetics research is defining an appropriate control group for comparing to the cases under study. Depending on the study design, addiction phenotypes can prove tricky. For example, one may want to identify genetic factors in highly dependent cases compared to controls. Using "never exposed" controls will produce very different results than if the controls have been carefully chosen to include those who have been exposed to some defined amount of substance use, but did not become addicted.

Differences in culture, religion, and laws sometimes can be exploited to delineate genetic factors that may be informative for improving addiction prevention and treatment. On a population level, those societal differences can be considered as

"macrophenotypes." Macrophenotyping allows the use of statistics and demographics for a given population without knowing the specific phenotypes of its individuals (Table 3.1). For example, the legal drinking age differs across the globe. Some Islamic nations prohibit drinking alcohol at any age. In other countries, the minimum age for consuming alcohol legally differs from the age when it can be purchased legally. Thus, laws and religious practices governing alcohol use serve to produce a macrophenotype. The age of legal smoking also differs somewhat from one country to the next. A recent survey of three billion individuals in 16 countries found that 48.6 % of men and 11.3 % of women were tobacco users, a macrophenotype defined by gender (Giovino et al. 2012). In Nigeria, smoking is illegal in public, and the macrophenotype shows that the death rates due to smoking are the lowest globally (7.1 %). The anti-smoking culture in Nigeria is a powerful environmental constraint on smoking in the population. Those who nevertheless initiate smoking, therefore, might be genetically vulnerable to continue smoking and also have more difficulty quitting. Thus, an environmental constraint – cultural prohibition in this case – leads to a hypothesis that there may be rare but penetrant genetic variants that reside in Nigerian smokers. The most replicated genetic variants associated with nicotine dependence have been in the nicotinic acetylcholine subunit receptor genetic regions on chromosome 15 (see below). According to the International HapMap Project and the 1000 Genomes Project (see below), the variant primarily associated with smoking dependence is nonexistent in the Yoruba (Nigerian) population, rare in Americans of African ancestry, and common in Americans of European ancestry (Fig. 3.1). This raises the possibility that genetic variants in Nigerian smokers could illuminate new drug targets for smoking cessation and lead to better treatment and intervention approaches.

3.2.3 Genetics and Epigenetics

At the molecular level, genetic approaches examine the structure and function of DNA and how genetic variation affects the expression of the genetic information. The hope of understanding the molecular basis of drug addiction and other complex phenotypes is driven, in part, by the remarkable progress that has been made in the field of genetics during the past decade. The year 2013 marks the tenth anniversary of the sequencing of the human genome. As a result, we know that humans share approximately 99.6 % of the three billion nucleotides of DNA sequence. Our genetic individuality lies in the remaining 0.4 % (approximately 12 million) nucleotides that comprise genetic differences largely represented by single-nucleotide polymorphisms (SNPs), copy number variations, as well as small insertions and deletions that are scattered across the genome. SNPs are the most well-studied variations and are generally benign with unknown consequence, but some may account for trait differences that alone, or in combination, contribute to disease (Barreiro et al. 2008). Approximately six million SNPs are quite common with allele frequencies greater than 10 % in the population. Others are of moderate frequency (1–10 %), and many are rare (<1 %).

Table 3.1 Alcohol, cigarette, and drug use macrophenotypes across the HapMap countries. Ranges were determined for all countries (bottom row) and then assigned a colored quartile (low, medium-low, medium-high, and high). HapMap countries represent four populations that have genotype and haplotype data in the public domain available for download: Ibadan, Nigeria (YRI); US residents of northern and Western European ancestry (CEU); Tokyo, Japan (JPT); and Han Chinese individuals from Beijing, China (CHB). Countries in the Northern Europe and Western Europe regions are separated for purposes of illustrating the macrophenotypes

HapMap country		Purchase age for alcohol	Alcohol consumption L/capita/year	Alcohol death rates per 100,000	Purchase age for smoking	Number of cigarettes per adult per year	Percentage of All deaths attributed to Smoking in the year 2000	Drug use death rates per 100, 000
Nigeria (YRI)		18	9.78	0.8		103	2.3*	2
Japan (JPT)		20		0.2	20	2,028	12	0
China (CHB)		18	4.21	0.6		1,648	11.5*	0
United States (CEU)		21	8.44	1.6	18	1,196	21	1.5
Northern Europe (CEU)								
	Denmark	16	11.37	9.9	18	1,495	22	0.5
	Estonia	18	13.77	9.2	18	1,718	15	0.3
	Finland	18	9.72	2	18	956	10	0.5
	Iceland	20	5.91	1.2	18		18*	0.2
	Ireland	18	13.39	0.9	18	1,391	18	1.8
	Latvia	18	9.5	3.1	18	1,890	13	1.4
	Lithuania	18	12.03	1	18	920	12	0.5
	Norway	18	6.21	2.8	18	493	12	0.6
	Sweden	18	6.7	2.1	18	751	9	1.3
	United Kingdom	18	11.67	1.1	18	790	19	2.1
Western Europe (CEU)								
	Austria	16	12.6	3.4	16	1,684	12	2.9
	Belgium	16	9.7	2.1	16	1,763	18	0.5
	France	18	13.3	4	18	876	11	0.4
	Germany	16	11.81	3.9	18	1,125	13	0.8
	Luxembourg	16	13.01	2.8	16		15	0.7
	Netherlands	16	9.55	0.9	16	888	18	0.1
	Switzerland	16/18	10.56	1.8	16/18	1,698	12	1.9
	global range	15–21	0–15	0–25.1	16–21	0–3,017	2.3–22	0–29.1

Low
Medium low
Medium high
High
Not available

Alcohol data (purchase ages): http://www.icap.org/table/MinimumAgeLimitsWorldwide; (consumption): http://www.who.int/substance_abuse/publications/global_alcohol_report/msbgsruprofiles.pdf and http://en.wikipedia.org/wiki/List_of_countries_by_alcohol_consumption; (death rates): http://www.worldlifeexpectancy.com/cause-of-death/alcohol/by-country/
Smoking data (purchase ages): http://en.wikipedia.org/wiki/Smoking_age; (consumption): http://en.wikipedia.org/wiki/List_of_countries_by_cigarette_consumption_per_capita; (death rates): http://www.ctsu.ox.ac.uk/deathsfromsmoking/

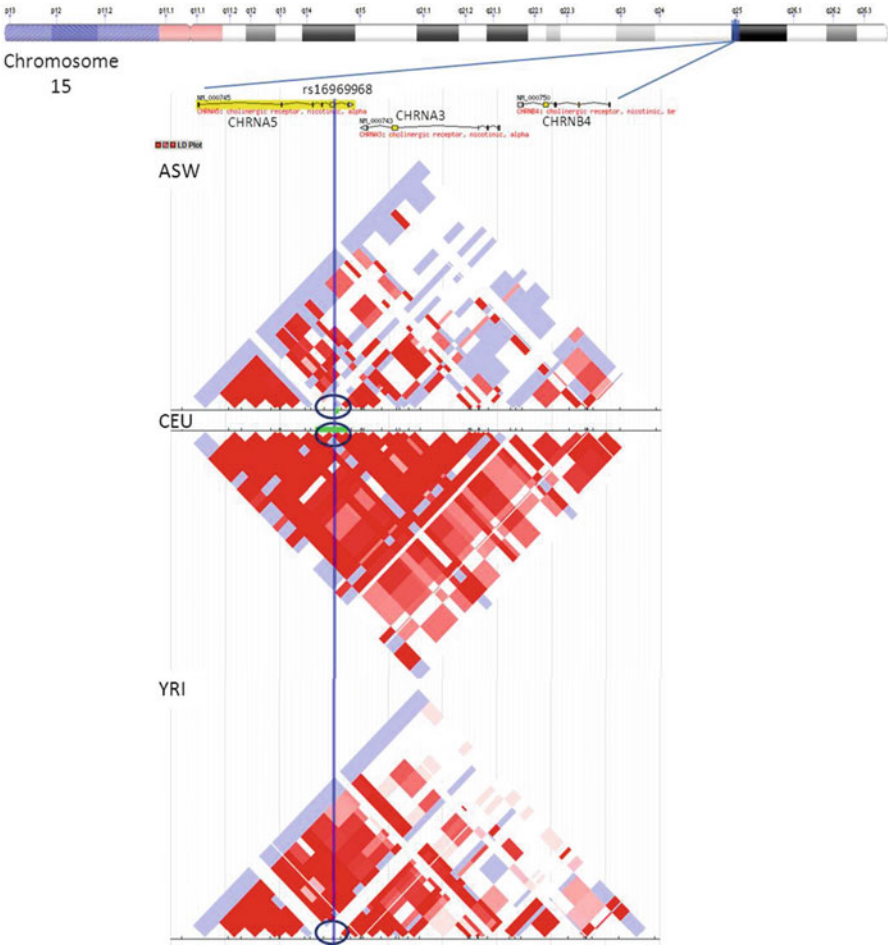

Fig. 3.1 Linkage disequilibrium (*LD*) plots for the CHRNA5/A3/B4 region on chromosome 15. The orientation of the CHRNA5, CHRNA3, and CHRNB4 genes is shown as the expanded section underneath the full chromosome 15 map (*top*). The vertical *blue line* represents the rs6969968 SNP and intersects the LD plots from the following populations: Southwestern US residents with African ancestry (ASW; *top*), US residents with European ancestry (CEU; *middle*), and Ibadan, Nigeria (YRI; *bottom*). The *green line* within the *blue circles* indicates the region of LD. Note the high LD in the CEU population (*long green line*), the very low LD in the ASW population (*short green line*), and the lack of LD in the YRI population (no *green line*). The LD plots were generated using the HapMap Data Phase III/release #2, February 09 on NCBI B36 assembly, dbSNP b126:chr15: 76,640,000 to 76,730,000 (http://hapmap.ncbi.nlm.nih.gov/cgi-perl/gbrowse/hapmap3r2_B36/)

Progress in the field of genetics during the past 20 years has come through conceptual insights and technological breakthroughs that have produced powerful approaches for rapid and robust screening of millions of known SNPs. Two key discoveries revolutionized the field. The first was the recognition that the genome had specific regions with higher recombination rates, the so-called recombination

hot spots. The second was the finding that the genome is organized into block-like structures or haplotypes that can be "tagged" by SNPs.

Recombination hot spots exploit how the process of inheritance relies on the basic molecular structure of DNA, rather than on the sequence variation in it. This has great implications on the nonrandom patterns of DNA sequence variation along chromosomes, which, in turn, can be used to reveal useful DNA sequence variation that contributes to disease (Hey 2004). Linkage disequilibrium (LD) describes the nonrandom association of alleles at adjacent locations on the chromosome, or loci. The farther apart two loci are, the more likely they are to recombine. Genomes with low LD are older, where there has been a longer period of time for recombination events to occur (haplotypes are shorter and made up of fewer SNPs), such as seen in the African populations. On the other hand, populations with higher LD are the newer populations such as the European Americans and isolated populations such as the Ashkenazi Jews (Shifman et al. 2003).

The second discovery was that these LD block structures acted as fingerprints for geneticists who could use them to identify correlated SNPs across the genome (Altshuler et al. 2008; Trifanova et al. 2012). In other words, one or a few SNPs could represent an entire haplotype (because of the high rate of LD), which meant that rather than screening the entire SNP collection across the genome, only a subset of proxy SNPs – or TagSNPs – needs to be screened without loss of information. From this concept, the NIH International HapMap Project was launched to describe the common patterns of 3.5 million SNPs across populations (The International HapMap Consortium 2005, 2007). The HapMap Project has been an invaluable tool for SNP genotyping platform improvements and for helping to discern the importance of genetic association loci for complex diseases. Subsequently, the 1000 Genomes Project was launched with the goal of characterizing 95 % of genetic variation accessible by high-throughput sequencing technologies and that have 1 % or greater allele frequency in each of five major population groups, including Europe, East Asia, South Asia, West Africa, and the Americas (The 1000 Genomes Project Consortium 2010, 2012). Together, these represent the most extensive collections of human genomic diversity to date and provide a necessary piece to the puzzle for understanding how genetic diversity impacts disease. The HapMap and 1000 Genomes data were intended to be a resource used for identifying and cataloging genetic similarities and differences in humans, and therefore, these datasets do not have phenotypic information. However, as illustrated in Table 3.1, they may be useful for initial macrophenotypic assessment, to then apply to standard case control studies for the purposes of associated genotypes to phenotypes.

The structure of LD in distinct genomic sites, such as those we know or suspect to be associated with addiction, is of interest. The LD structure defines the boundary of a given region. The more population structures one can access (e.g., through HapMap), the better and narrower those boundaries are defined (Fig. 3.1). A narrow region is central to this approach because once an initial SNP has been associated with a disease phenotype, it represents much more of the genetic variation than just that SNP alone. The importance of the sequence

contained within these regions then becomes the analytic quest, and finding the genetic variation within that LD block that has functional significance is the next step in understanding the inherited component of addiction susceptibility. Replication is imperative; candidate SNPs that have been evaluated repeatedly across ethnicities and in a variety of association study settings will help to isolate those variants more likely to show functional effects (Saccone et al. 2008).

Genome-wide association (GWA) studies have been the cost-effective approach of choice for discovering important genetic regions in complex diseases. The GWA approach is built on the notion that common alleles predispose to common disease. Current GWA genotyping platforms include common SNPs derived from haplotype information to allow for genotyping the most SNP content across ethnicities. However, the genomic coverage for the GWA genotyping platforms was not selected for specific hypotheses; thus, it is important to understand the coverage a genotyping array provides (Saccone et al. 2009b) and to replicate and verify any and all findings. Most GWA studies to date – about 75 % of them – have been performed in populations of European descent. Of those that examine non-European populations, the numbers of individuals represented within them are predominantly from European descent (Rosenberg et al. 2010). As non-European populations become accessible for GWA analysis on a variety of traits, it will be possible to test the generalizability of the GWA findings from European populations to others. Cross-population contrast mapping (Saccone et al. 2008; Helgason et al. 2007; Liu et al. 2012) compares genotype frequencies at the associated SNP and the correlated SNPs within the haplotype to define the genetic architecture for both populations at that locus (Rotimi and Jorde 2010; Saccone et al. 2008; Zaitlen and Eskin 2010). This approach relies on the assumption that biological mechanisms underlying a given disease are shared across populations, despite the differences in allele frequencies.

A good example of this approach comes from nicotine dependence studies. In 2007, a group of scientists from both the public and private sectors embarked on a small GWA study ($n \sim 2{,}000$) for nicotine dependence that compared nicotine-dependent individuals ("cases") with exposed (must have smoked at least 100 cigarettes during lifetime), but not addicted, controls (Bierut et al.). The cases and controls were of European American descent and their genotypes were compared across 2.2 million SNPs. From the final analyses (Bierut et al. 2007; Saccone et al. 2007), several SNPs were identified in the nicotinic subunit receptor genes that had not been well studied previously. These genes are in a cluster on chromosome 15, CHRNA5 (alpha 5), CHRNA3 (alpha 3), and CHRNB4 (beta 4), referred to here as the CHRNA5/B4/A3 cluster. Previous work using pharmacological methods had identified CHRNA4 and CHRNB2 as the main culprits involved in smoking dependence, which have been the primary targets for smoking cessation medications. The GWA study data, however, has broadened the scope to other nicotinic subunit receptors in the larger nicotinic subunit receptor family. The SNP that was most interesting was rs16969968 because it represented a change from a conserved aspartic acid at position 398 to an asparagine (D398N) within the CHRNA5 receptor subunit (Bierut et al. 2008).

At the nucleotide level, the A allele of the SNP is the risk allele, and the G allele is the ancestral, or common, allele (Fig. 3.1). The fact that this SNP was in the part of the gene that encoded the protein and that it was conserved across species added impetus to studies seeking to replicate the finding and examine the functional consequences of the SNP.

As one of the most replicated findings in complex disease genetics, however, it remained unclear if it would withstand cross-population analyses. This region has high linkage disequilibrium in European ancestry populations, making it difficult to differentiate correlation from causation. It turns out that the frequency of rs16969968 varies widely across 39 different populations (Cann et al. 2002). Ultimately, a meta-analysis for nicotine dependence in tens of thousands of samples of European ancestry confirmed the CHRNA5/B4/A3 cluster association (Thorgeirsson et al. 2010; Tobacco and Genetics Consortium 2010; Liu et al. 2010). In populations of European and Middle Eastern origin, the frequency of the A allele was around 40 %, whereas it was uncommon or absent in East Asian, Native American, and African and African American populations (Fig. 3.1 and Bierut et al. 2008; Saccone et al. 2009). Although the rs16969968 risk variant is a strong association, it only explains a small amount of variance (Berrettini and Doyle 2012). Others have used GWA meta-analysis as a way to identify other loci involved in smoking dependence in European ancestry populations (Thorgeirsson et al. 2010) and in African American populations (David et al. 2012) and have found additional variants of interest, although not as strong. Genome sequencing methods are needed to look for potential rare variations with large effects that are missed by the GWA platforms that have been employed to date.

Because the genetic architecture of the CHRNA5/B4/A3 cluster varies across populations, comparing associations across diverse populations with differing genetic architectures can help refine the region of association and point to variants more likely to have functional relevance (Rotimi and Jorde 2010; Saccone et al. 2008; Zaitlen and Eskin 2010). Multiple genome-wide and targeted association studies now have revealed significant associations between nicotine dependence and variants in the CHRNA5/A3/B4 cluster in subjects of European origin and Asian (Li et al. 2010) and African American ancestry ($n = 32{,}587$), which extends the involvement of this specific gene cluster across all three populations, narrowing the region of association (Chen et al. 2012b). Of the variants tested, only rs16969968 was associated with smoking in these three populations and was a marker of a larger "high risk" haplotype. The consistently observed association of rs16969968 with heavy smoking across multiple populations, combined with its known biological significance, suggests that rs16969968 is most likely a functional variant that alters risk for heavy smoking. Implications of this work will be explored in subsequent sections.

The molecular intersection where the environment meets the genes happens at the epigenome and is worth mentioning here. Epigenomics is the study of functional, and sometimes heritable, changes in the regulation of gene activity and expression that are not dependent on gene sequence (Chadwick 2012).

Although each cell type in the human body effectively contains the same genetic information, epigenetic regulatory mechanisms enable pluripotent stem cells to give rise to the diversity of differentiated cell types (e.g., skin cells, liver cells, or neurons).

Genome function and cellular phenotypes are influenced by DNA methylation, along with histone modifications, which account for associated proteins that activate or repress the genome function in a context-dependent manner (Bernstein et al. 2010). Chromatin is the combination of DNA wrapped around histone proteins (called nucleosomes) and associated with DNA-binding factors, accessory complexes, and noncoding RNAs. Chromatin structure allows the tightly packed DNA to fit into the nuclei, yet it retains the ability to react dynamically to the specific gene expression needs of the cell. In states of activity, DNA is loosely packaged so that specific genes are readily accessed by the transcription machinery and "turned on." In states of inactivity, DNA is wrapped around the histones and "turned off" by structural proteins that ensure the chromatin-containing genes are tightly packed and inaccessible to the transcriptional machinery. This "winding" and "unwinding" of chromatin occurs through chemical modifications such as methylation and acetylation on the histone proteins or to the DNA itself (e.g., DNA methylation or hydroxymethylation) that take their cues from elsewhere, whether that be from the cellular, social, or even historical environment. There have been several human studies indicating that ancestral environments can dictate the physiology and behavior of descendants (Kaati et al. 2002).

A 2004 seminal report demonstrated the concept that parenting and early environmental exposures (e.g., exposures to the gamete, fetus, or offspring) or experiences influence risk for later life pathologies, and these can be unequivocally linked to epigenetic changes (Weaver et al. 2004; Johnstone and Baylin 2010). In rats, maternal behaviors such as licking and grooming can epigenetically "program" stress responses in the pups that are stably maintained in adulthood. The research demonstrated that offspring of mothers displaying high levels of maternal care showed different DNA methylation patterns in the brain's stress pathways and exhibited fewer anxiety-like behaviors compared to offspring of mothers displaying low-level maternal care, resulting in pups with higher anxiety-like behaviors. Interestingly, the researchers went on to demonstrate that the effects were reversed in cross-fostering experiments (Weaver et al. 2004).

Similarly, exposure to drugs of abuse also may have epigenetic influences that affect the offspring (Kendler et al. 2012). In a recent study, male rat offspring, but not female rats, sired by cocaine-exposed males were slower to acquire cocaine self-administration and maintained lower rates of responding for cocaine than in offspring sired by unexposed males. The investigators went on to show that the effects were likely due to increased acetylated histone H3 with brain-derived neurotrophic factor promoter regions in the sperm of sires that self-administered cocaine (Vassoler et al. 2013). Taken together, these examples indicate the pervasive influence of environmental factors that regulate epigenetic mechanisms and that these influences may not only affect cellular events, but they may affect cellular events that take place in our children and grandchildren.

Not unlike the HapMap and the 1000 Genomes Projects that came before it, the NIH Roadmap Epigenomics Program and the International Human Epigenome Consortium (IHEC) are developing atlases of the epigenomic landscape of a variety of cell types (Chadwick 2012). Scientists have been collecting data to generate maps of the epigenomic landscape of a variety of tissue types, but there has been little done to date looking at individual differences and their effects on epigenomic programming. With the epigenomic maps at hand, it will be possible to understand influences of drugs of abuse, stress, and diet on epigenetics and then to consider how environmental context and culture can affect the epigenome as well. While genetic variation is more tractable to screen, epigenetic variation may lead to more effective treatment approaches since the mechanisms may be more malleable than our DNA.

3.2.4 Gene × Environment Interactions and Prevention

An understanding of addiction genetics will improve our ability to predict who is at risk for drug addiction and who is not. With improved predictive validity, prevention efforts can be focused on those at high risk. To reiterate a point made earlier, vulnerability to drug addiction is the result of multiple genes interacting with one another (epistasis or G × G interactions), genes interacting with environments (G × E), and genes interacting with environment and stage of development (G × E × D). Although challenging and costly, research employing designs and analyses that enable the study of these interactions is critical to our progress. There are statistical models available that enable us to characterize such complex interactions (Neale et al. 2006). Structural equation modeling, for example, allows variables that are not measured directly (i.e., latent factors) to be incorporated. This is an important consideration for addiction phenotypes since not everyone will try substances of abuse, let alone become addicted. Moreover, replicating complex designs is itself a challenge and can be approached in two general ways. Direct replications are those which use the same statistical model on the same outcome variable, genetic variant, and environmental factor as was done for an original finding. Indirect replications seek to replicate the general finding but use different variables (Duncan and Keller 2011).

As an obvious example of G × E interaction, consider that the CHRNA5/B4/A3 cluster associated with nicotine dependence will be penetrant only if the person is exposed to tobacco. This example provides a straightforward explanation for why one person who has the risk variant may become dependent on tobacco and smoke upwards of 30 cigarettes/day, while another person who does not have the risk variant may try a cigarette and never use tobacco products again (Duncan and Keller 2011). Indeed, much of the success in decreasing smoking prevalence, for example, has been realized through well-supported environmental and educational methods. Trends for smoking have declined since 1970, but have plateaued since 1990. This suggests that these strategies alone are not as effective in current smokers, indicating that current smokers and many future smokers

may be a more genetically at-risk population. Nearly 90 % of smokers who try to quit relapse within a year, with the majority relapsing within a week (National Institute on Drug Abuse 2012). Therefore, treatment and prevention interventions for substance abuse disorders and other complex diseases will have maximum public health benefit when multifaceted approaches incorporating the genetic, biological, and environmental determinants are employed (Merikangas et al. 1998).

A recent example of G × E × D interaction comes from two independent reports (Weiss et al. 2008; Hartz et al. 2012) demonstrating a strong association between CHRNA5/A3/B4 variants and increased severity of nicotine dependence in early-onset smoking. The study extends the original association by separating the heavy smokers into two groups, those with "early onset" of daily smoking at or before age 16 and those with "late onset" on or after age 17. The association was seen in subjects who began daily smoking at or before the age of 16, thus identifying a period of exposure vulnerability that may contribute to nicotine dependence later in life. This report demonstrates a clear interaction among genes, environment and development where the confluence of factors increases the likelihood of nicotine dependence. It also supports other evidence that people who use addictive substances before age 18 are six times more likely to develop a substance use disorder than those who do not start using until they are 21 or older (CASA 2011).

Other environments influence addiction behaviors, too. Partner smoking is a risk factor for smoking (Sutton 1993). Among women who quit smoking during pregnancy, the strongest predictor of relapse was having a partner who smoked. Another study found relapse rates four times as high for individuals living with smokers, compared to those who did not (Kahn et al. 2002), and women may be more vulnerable to spousal influences than men (Homish and Leonard 2005).

Another study found that individuals with the rs16969968 risk allele who received low parental monitoring were at increased risk for nicotine dependence (Chen et al. 2009). Counterintuitively, peer smoking had a substantially lower effect on nicotine dependence among those with the high-risk rs16969968 genotype than among those with lower-risk genotypes (Johnson et al. 2010). This research highlights the possibility that those with high genetic risks may be more or less affected by intervention strategies based upon familial and/or social contexts. G × E influences such as these examples vary widely across cultures, and understanding these types of environmental influences can be of great help in developing robust prevention and intervention strategies that can be tailored to individuals.

3.2.5 Neurobiology

One of the problems of drug abuse is its ability to "hijack" the brain's reward system. Drug users will go to great lengths to seek a high. The discovery of gene variants that confer vulnerability to addiction promises to improve our

understanding of the neural processes responsible for addictive behaviors. Repeated exposure to some drugs results in enhanced responses to the drug (i.e., sensitization) and is a hallmark of addiction. Through repeated exposure, there is an enhancement of dopamine release across the rewarding centers of the brain (nucleus accumbens, ventral tegmental area, and the frontal cortex), resulting in reinforcement of drug taking. Neurobiological studies examining nicotine self-administration in animal models support the notion that CHRNA5 acts as a "gate" for nicotine intake, but not necessarily by acting to enhance the reward pathway, but rather by abolishing an aversive circuit through the medial habenula and interpenduncular nucleus (IPN; Fowler and Kenny 2012). Gene expression studies in mice show that the CHRNA5/A3/B4 genes are expressed in the habenular/IPN regions, unlike the more global expression of other nicotinic subunit receptors (Fig. 3.2 and Changeux 2010). In animals where the CHRNA5 gene has been knocked out, the "gate" is missing and self-administration of nicotine increases. Additionally, virus-induced expression of the CHRNA5-subunit-risk allele in the medial habenula-IPN nucleus of the rat resulted in reduced aversion to nicotine and, consequently, greater consumption of the drug (Fowler et al. 2011). Together, these findings provide neurobiological confirmation for what is seen in human genetics of nicotine dependence in that the heaviest smokers generally have the associated risk allele. Of course, so far these studies are not completely analogous inasmuch as knocking out the CHRNA5 gene in mice is not the same as a single nucleotide difference at the rs16969968 variant allele in humans, but trends pointing in the same direction are encouraging.

Another genetic variant, A118G in the human mu opioid receptor gene (MOR), has been associated with opioid, alcohol, and other drug addictions and with the need for higher morphine doses to achieve adequate analgesia in those who have this allele. Recent work using animal- and human-cultured cell lines found that the asparagine (G allele) reduced N-linked glycosylation more than the aspartic acid (A allele) form (Huang et al. 2012). This difference in glycosylation status causes protein instability and may account for the reduction of the MOR protein in certain brain regions. Other work has examined this gene variant's effects on dopamine release after tobacco smoking. One study shows that carriers of the G allele had more dopamine release in response to smoking than homozygous A-allele carriers. In addition, plasma cortisol levels were lower in G-allele carriers. These studies are consistent with literature on the association of MOR A118G with drug abuse and stress, yet continued research is needed to explore the implications of these findings to link these mechanisms to drug abusing behaviors.

Drug addiction is comorbid with many psychiatric conditions, such as depression, anxiety, and schizophrenia (Buckley et al. 2009). The high prevalence of cigarette smoking among schizophrenics suggests the hypothesis that addictive behavior and schizophrenia may rely upon shared neurocircuitry. For instance, approximately 90 % of people with schizophrenia smoke and use nicotine as a mechanism of self-medication to increase cognition (Chambers et al. 2001). Schizophrenics may have underlying genetic differences in regions of the brain that are similar to those seen in long-term substance users, but without the prior drug exposure. This example

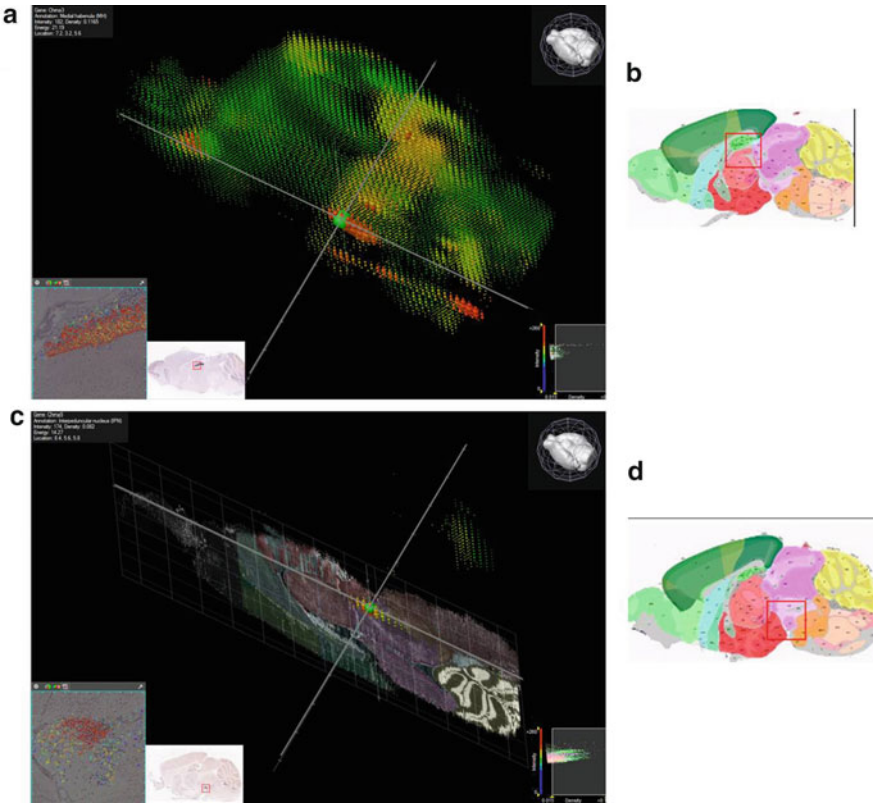

Fig. 3.2 Gene expression of CHRNA5/A3 in the medial habenula-interpenduncular nucleus (*IPN*). Gene expression data were obtained using the Allen Mouse Brain Atlas, released March 7, 2013: http://www.brain-map.org/. (Panel **A**): Gene expression of CHRNA3 in the medial habenula (*MH*). The orientation of the brain image is shown in the circular image on the *upper right*. The scale of intensity is shown on the *bottom right*. The axis crosses at the medial habenula and the gene expression is shown in the *bottom left*, adjacent to the in situ hybridization (*ISH*) image. (Panel **B**): Mouse brain anatomy map of selected region for CHRNA3 expression. *Panel C*: Gene expression pattern of CHRNA5 in the IPN. The axis crosses at the IPN and the gene expression is shown at the *bottom left*, adjacent to the ISH image. (Panel **D**): Mouse brain anatomy map of selected region for CHRNA5 expression

highlights the importance of studying the genetics of substance use and schizophrenia as distinct and as comorbid disorders. Additional studies have demonstrated novel associations between other gene variants in the CHRNA5/B4/A3 cluster with various smoking-related phenotypes, such as nicotine dependence symptoms, nicotine tolerance, smoking initiation, and comorbid conditions (e.g., regular drinking and depression), with these vulnerabilities being heightened in early-onset smokers. Once a gene variant is discovered and validated, a systematic analysis of the functional role that a gene variant plays can be undertaken.

3.2.6 From Treatment to Pharmacogenetics

Elucidating the genetic and neurobiological basis of addiction, from gene expression to the neural networks that mediate drug seeking and drug taking, eventually will enable scientists to translate knowledge into new treatments directed at specific targets in the brain or to treatment approaches that can be individualized for each patient (i.e., pharmacogenomics). Drawing a precise molecular portrait of addiction is challenging, but every new finding provides an unprecedented opportunity to identify and investigate new potential pharmacological targets or explore and exploit their clinical utility. For example, recent research has solved the crystal structure of the four opioid receptors (Wu et al. 2012; Thompson et al. 2012; Granier et al. 2012; Manglik et al. 2012). Although the opiate receptor has been studied for decades, the availability of its structure now provides a molecular framework for structure-based discovery of new medications with targeted pharmacological properties (Thompson et al. 2012). Understanding how these potent ligands work in the context of their effects on receptors with known genetic variation (e.g., the A118G variant mentioned previously) will enable medicinal chemists to design medications to maximize their therapeutic efficacy while minimizing their adverse side effects and abuse liability.

Genetic variation is the key to explaining individual differences in the way that drugs are distributed and metabolized. Pharmacogenetics/pharmacogenomics is the study of how genetic variation among individuals affects their capacity to metabolize drugs (pharmacokinetics) and the drugs' effects on the individuals (pharmacodynamics) (Rutter 2006; Belle and Singh 2008). There is significant variability in response to drugs of abuse, and pharmacogenetics provides relevant crossover concepts that tailor a person's genetic makeup to a drug treatment that provides the best "match."

Investment in genetics is bearing fruit for the development of treatment options for substance dependence. The A118G mu-opioid receptor polymorphism has been shown to be associated with therapeutic response to naltrexone treatment for alcohol dependence (Chamorro et al. 2012). This pharmacogenetic finding has important implications for targeted treatment of alcoholism in individuals with the 118G variant (Chamorro et al. 2012; Kranzler and Edenberg 2010). Recent meta-analysis on the A118G SNP of OPRM1 shows that naltrexone-treated patients carrying the G allele have lower relapse rates when compared to those homozygous for the A allele (Chamorro et al. 2012). The frequency of the G allele differs across populations; in Caucasians, it ranges from 15 % to 25 %, and in Asians, it is ~60 %. The potential impact of genetic screening prior to treatment in these ethnicities warrants consideration. Clinicians and patients may benefit from knowing that people homozygous for the A allele are not likely to respond to naltrexone.

A similar case can be made for pharmacogenetics of smoking. Nearly half of the people who smoke want to stop; however, most attempts fail, whereby only about 10 % of individuals achieve abstinence for 6 months or more (Ramoni et al. 2009). And, nicotine dependence contributes to the failure rate, with more highly dependent smokers having greater difficulty quitting – and staying abstinent

(John et al. 2004; Xian et al. 2005). There is growing evidence that interactions between smoker characteristics, medications, and quit success may help personalize the handful of medications that can be prescribed to a given smoker.

Cytochrome P450 (CYP) 2A6 is largely responsible for metabolizing nicotine to cotinine, and CYP2A6 genotypes contribute to variable metabolism rates that are seen across ethnicities (Nakajima et al. 2006) and even gender (Lee et al. 2012; Mwenifumbo and Tyndale 2007). Genetic variation in the CYP2A6 gene can increase or decrease the pharmacokinetics of the enzyme activity through altering the protein's expression level or its structure and function. Further studies show that the rate of nicotine metabolism predicts which smokers will be more successful at quitting with bupropion (Patterson et al. 2008) or nicotine replacement therapy (Malaiyandi et al. 2006; Schnoll et al. 2009). In the highly dependent smokers, a combination therapy is most beneficial (Loh et al. 2012).

In addition to the pharmacokinetic gene variations, pharmacodynamic gene differences are also important. The nicotinic subunit receptor B2 has been implicated in smoking cessation (Conti et al. 2008), as have the CHRNA5/B4/A3 cluster variants – although less robustly associated with cessation outcomes than with measures of smoking quantity. However, those that do show an association have shown that the same genetic risk variants that contribute to smoking quantity and nicotine dependence also predict smoking cessation (Chen et al. 2012). Carriers of the high-risk CHRNA5/A3/B4 haplotype were three times more likely to respond to smoking cessation medications, making this haplotype of interest for personalized cessation therapies. A series of randomized clinical trials grouped by smoking cessation therapy (NRT, varenicline, bupropion, and placebo) examined the association of CHRNA5/B4/A3 cluster variants with abstinence at the end of treatment and at 6 months after the quit date. In this study, treatment-seeking smokers with the CHRNA5/A3/B4-risk alleles (compared to those without) were less likely to achieve abstinence at 6 months if prescribed placebo, but more likely to achieve 6-month abstinence with treatment (Bergen et al. 2013).

Clinical trials assessing the joint effects of both the pharmacokinetic gene variations (CYP2A6) and the pharmacodynamics gene variations (CHRNA5 and others) are needed. Early investigations into the feasibility, cost-effectiveness, and impact of using genetics to tailor treatments in a real-world clinical setting have been promising (McClure et al. 2013). Larger studies are needed to understand the generalizability of this type of personalized intervention for smoking cessation.

3.3 Conclusion

Addiction is a complex, diverse, and dynamic disease. Progress in understanding, preventing, and treating addiction demands a multifaceted research program requiring analytic endurance that considers the interactive influences of genes, environment, development, and culture. The scientific advances have been fueled in part by recent advances in genomics and molecular biology. The science of epigenetics has

yielded exciting findings already and promises to unlock the ages-old gene-environment conundrum.

A major challenge awaiting resolution is the translation of basic science discoveries into novel prevention strategies and effective treatment approaches. As discussed above, discoveries in genomics and neuroscience have opened up new vistas for exploration. New medications built upon scaffolds designed computationally to fit ever more precisely specified crystalline structures of brain receptors herald an era of designer treatments for addiction. And treatment approaches that capitalize on genomic information about an individual's metabolic profile signal a pharmacogenetic approach to guide medical and treatment decisions.

NIDA has made understanding the interaction among genes, environment, and development a cornerstone of its agenda. The G × E × D interaction is thorny, and research is beginning to tease apart the separate and combined effects of these factors, but there is still challenging work to be completed. Emerging areas, including systems biology, epigenetics, computational approaches, and the role of social context or culture in drug addiction will be important research priorities for funding agencies across the globe. Future gene-based analyses combined with environmental interventions have great potential to combat addiction and save lives. The opportunities offered by global approaches can strengthen these needed research programs and hasten that goal.

Glossary of Terms

Allele An alternative form of a gene that is located at a specific position on a specific chromosome

Epigenetics The study of heritable or long-term alterations in gene expression that are not caused by changes in DNA sequence

Gene A specific segment of DNA on a chromosome that is responsible for specific characteristics in an organism

Genetic variation Differences or variations in alleles of DNA segments (e.g., genes) that occur both within and across populations

Genetics The science of genes, heredity, and variation in living organisms

Genome-wide association study (GWA or GWAS) A method to examine many common genetic variations in different individuals to see if any variant is associated with a trait

Genotype An individual's collection of genes and alleles

Haplotype Combinations of alleles at adjacent locations on a chromosome that are inherited together

Heritability The proportion of observable differences in a trait within a population that is due to genetic differences

Histone A family of basic proteins that associate with DNA to pack the DNA into chromosomes

Linkage disequilibrium (LD) The nonrandom association of alleles at two or more loci

Macrophenotype Using global statistics or demographics to estimate the phenotype of a given population without knowing the specific phenotypes of individuals within that population

Nucleotide The basic building block of nucleic acids (i.e., DNA and RNA)

Pharmacogenetics Genetic differences in genes that affect an individual's response to drugs

Phenotype The observable physical or biochemical characteristics of an organism, which are influenced by both genetic makeup and environmental influences

Recombination The formation of new combinations of genes in progeny that did not occur in parents

Single-nucleotide polymorphism (SNP) A DNA sequence variation that occurs at a single nucleotide in the genome

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Burden of Disease: The Epidemiological Aspects of Addiction

4

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Abstract

This chapter provides and overview of the epidemiological aspects of substance use disorders. Starting with a methodological introduction into the estimation of global burden of disease for substance use disorders, this chapter subsequently reports regional differences in prevalence of substance use disorders and the resulting attributable burden. The chapter closes with a review of the factors that impact the incidence and course of substance use disorders.

Substance use disorders have been shown to account for about 1 % of the global burden of disease in 2010, as measured in disability-adjusted life years. The underlying methodology for this estimate was restricted to dependence and excluded abuse as defined in DSM-IV or harmful use as defined in ICD-10, so the most recent global burden of disease estimates for 2010 underestimate real burden, especially for alcohol use disorders.

The burden of disease attributable to different substance use disorders varies strongly across countries. High-income countries experience greater burden from alcohol as well as from most illegal drugs. However, burden increased in the past 20 years, especially in the developing world. North African and Middle Eastern countries experience the lowest burden of alcohol use disorders, probably due to religious reasons.

A large number of factors influence the course of substance use from initiation to the development of a substance use disorder. The overall picture suggests that extra-individual, social factors as the cultural background or peer behavior predominantly influence use initiation and transition to hazardous patterns of use, whereas intraindividual factors as personality features and genes become more prominent in the development and possible chronification of substance use disorders.

4.1 Global Burden of Disease Associated with Substance Use Disorders

Addictions (substance use disorders), as currently defined in major classification systems (see ▶ Chap. 5, "Changing Patterns of Drug Use in Georgia: A Case Vignette"), account for a considerable amount of the global burden of disease. In the 2010 Global Burden of Disease (GBD) study, alcohol use disorders were estimated to account for almost 1 % of the global burden of disease (0.7 %; see Table 4.1 and Murray et al. 2012). Burden of disease is defined here as a summary health indicator measured in Disability Adjusted Life Years (DALYs) lost (Murray 1996), comprised of years of life lost due to premature mortality plus years of life lost to disability (Vos et al. 2012). In addition to the global burden of disease from alcohol use disorders, there is about the same amount of burden of disease from illegal drug use disorders (0.8 %; see Table 4.1 and Murray et al. 2012), plus the burden from tobacco use disorders, which was not quantified in the 2010 GBD study.

Table 4.1 Burden of disease associated with substance use disorders and with substance consumption as a risk factor (GBD 2010 study)

	DALYs* in 1,000s					DALYs* per 100,000 persons				
	1990	95 % CI*	2010	95 % CI*	Delta*	1990	95 % CI*	2010	95 % CI*	Delta*
Disease categories										
Alcohol UD*	13,138	(9,544–17,484)	17,656	(12,923–23,243)	34.4 %	248	(180–330)	256	(188–337)	3.4 %
Drug UD*	13,152	(9,727–17,252)	20,016	(15,293–25,453)	52.2 %	248	(183–325)	291	(222–369)	17.1 %
Opioid UD*	5,284	(3,802–6,859)	9,165	(7,031–11,466)	73.4 %	100	(72–129)	133	(102–166)	33.5 %
Cocaine UD*	863	(531–1,321)	1,111	(650–1,740)	28.7 %	16	(10–25)	16	(9–25)	−0.9 %
Amphetamine UD*	1,912	(1,079–2,957)	2,619	(1,480–4,125)	37.0 %	36	(20–56)	38	(21–60)	5.4 %
Cannabis UD*	1,694	(1,118–2,415)	2,059	(1,345–2,972)	21.5 %	32	(21–46)	30	(20–43)	−6.4 %
Other drug UD*	3,401	(2,349–4,958)	5,062	(3,573–7,052)	48.8 %	64	(44–94)	73	(52–102)	14.5 %
Tobacco UD*	Not examined in GBD study 2010									
Risk factor										
Alcohol	73,715	(66,090–82,089)	97,237	(87,087–107,658)	31.9 %	1,390	(1,247–1,548)	1,411	(1,264–1,563)	1.5 %
Drug use	15,171	(11,714–19,369)	23,810	(18,780–29,246)	56.9 %	286	(221–365)	346	(273–424)	20.8 %
Tobacco	151,766	(136,367–169,522)	156,838	(136,543–173,057)	3.3 %	2,863	(2,572–3,198)	2,276	(1,982–2,512)	−20.5 %
All DALYs	2,497,280		2,482,260		−0.6 %	47,105		36,027		−23.5 %

* *DALYs* disability adjusted life years, *CI* confidence interval, *UD* use disorders, *Delta* percentage change between 1990 and 2010

4.1.1 Methodology of Global Burden of Disease Estimations

To understand the burden of disease estimates and their potential limitations, it is necessary to understand how they are estimated. The definition of substance use disorders used in the GBD study (Vos et al. 2012) excluded "harmful use" as defined in International Classification of Diseases 10th revision (ICD-10) (World Health Organization 1992) or "abuse" as defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV (American Psychiatric Association 2000). Thus, the main burden reported in Table 4.1 stems from dependence (fetal alcohol spectrum disorder is also included in this burden category). The exclusion of "harmful use" or "abuse" is important for two reasons. First, the estimates are conservative. Second, this exclusion impacts the estimates for alcohol versus drug use disorders; for alcohol contrary to drug use disorders, a large part of the disease burden is actually due to harmful use/abuse. While disability stemming from the abuse of alcohol is lower compared to dependence (Samokhvalov et al. 2010), the prevalence and incidence of alcohol abuse is higher in many countries, such as in the United States (Hasin et al. 2007; Grant et al. 2009; Kessler and Üstün 2008; Rehm et al. 2005). For disability stemming from the harmful use of alcohol, and for mortality associated with both harmful use and abuse of alcohol, there is a scarcity of good data globally; however, from the available data, and from the calculations of previous GBD studies (Rehm et al. 2004, 2009), where harmful use/abuse of alcohol was not excluded, we can conclude that a substantial underestimation of alcohol use disorders exists in the current GBD study. On the other hand, for drug use disorders, other than cannabis use disorders, the estimation methods for prevalence were often based on problem use as defined by the United Nations Office on Drugs and Crime (2012; Degenhardt and Hall 2012), which had been used for illegal drug use disorders including abuse before, and now they are used for disorders excluding abuse. Consequently, the difference between the burden of illegal drug use disorders as a disease condition and illegal drug use as a risk factor is not large (see Table 4.1); more than 80 % of the burden from illegal drugs as a risk factor derives from drug dependence.

Tobacco use disorders are a late addition to the category of substance use disorders. Only 50 years ago the World Health Organization (WHO) clearly separated the legal, habit forming drugs of alcohol and tobacco from addictive illegal drugs (World Health Organization 1957). It is now accepted that both alcohol and tobacco are addictive substances (as evidenced in the current classifications, e.g., chapter F17 of ICD-10: "Mental and Behavioural Disorders Due to Use of Tobacco"); however, in the case of tobacco, the psychiatric classification of tobacco use disorders never entered the mainstream epidemiology and burden of disease research. Thus, "tobacco use disorders" were not a disease category in the latest GBD study report nor for other burden calculations (e.g., Wittchen et al. 2011). While part of the burden of tobacco as a risk factor is due to tobacco use disorders, the exact proportion is unclear, but is likely higher than either of illegal drugs or alcohol (see Table 4.1).

Another important aspect of the interpretation of the global burden of disease numbers concerns the underlying epidemiology. The methodology underlying the estimates of the prevalence of illegal drug use disorders has already been described

(Degenhardt and Hall 2012). With respect to alcohol use disorders, prevalence was based exclusively on a systematic review of high-quality general population surveys which measured alcohol dependence using standardized measures such as the Composite International Diagnostic Interview (CIDI; first version by Robins et al. (1988); several versions currently in use, most importantly the CIDI of the World Mental Health Survey (http://www.hcp.med.harvard.edu/wmhcidi/instruments.php), the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Wing et al. 1990) or the AUDADIS (Grant et al. 1995)). Studies in several countries under the aegis of the WHO have revealed that for alcohol dependence as well as for illegal drug dependence standardized instruments yield similar diagnoses and, subsequently, prevalence rates; for harmful use or abuse, these similarities were much less pronounced (Üstün et al. 1997; Pull et al. 1997); however, even when standardized instruments are used, prevalence can differ. For example, consider the above-mentioned CIDI for the World Mental Health Surveys. In the first years, dependence items were only asked if the respondent had at least one abuse symptom, thereby leading to a huge underestimation of dependence prevalence (Grant et al. 2007). Similarly, small changes in wording seem to be responsible for substantive changes in Dutch prevalence figures of the past decade (see Rehm et al. 2012 for comparisons).

4.1.2 Regional Differences

Globally, the years of life lost due to both disability and premature mortality (measured in DALYs) due to alcohol use disorders and drug use disorders varied greatly by geography in 2010. See Figures 4.1 and 4.2 for the age-standardized DALYs per 100,000 people caused by alcohol use disorders and drug use disorders by country in 2010, respectively.

In 2010 the burden of alcohol use disorders was highest in Eastern Europe and in Central Asia, with 1,046 and 435 DALYs per 100,000 people being caused by alcohol use disorders in Eastern Europe and Central Asia, respectively. The lowest burden of alcohol use disorders was experienced in North Africa and Middle East, with 68 DALYs per 100,000 people caused by alcohol use disorders in 2010; religion (Islam is the main religion in most countries of this region) was the main factor that influenced the magnitude of the burden of alcohol use disorders in the North Africa and Middle East region. The country that experienced the greatest burden of alcohol use disorders in 2010 was Belarus, with 1,272 DALYs per 100,000 people caused by alcohol use disorders. For comparison, the global burden of alcohol use disorders in 2010 was 256 DALYs per 100,000 people.

In 2010 the burden of drug use disorders was highest in North America (high income), Australasia, and Eastern Europe, with 676, 573, and 465 DALYs per 100,000 people caused by drug use disorders in 2010 in North America (high income), Australasia, and Eastern Europe, respectively. The largest burden of drug use disorders was observed in Equatorial Guinea and the United Arab Emirates, with 1,001 DALYs and 843 DALYs per 100,000 people, respectively, caused by drug use disorders in 2010. With respect to the burden of specific drug use disorders,

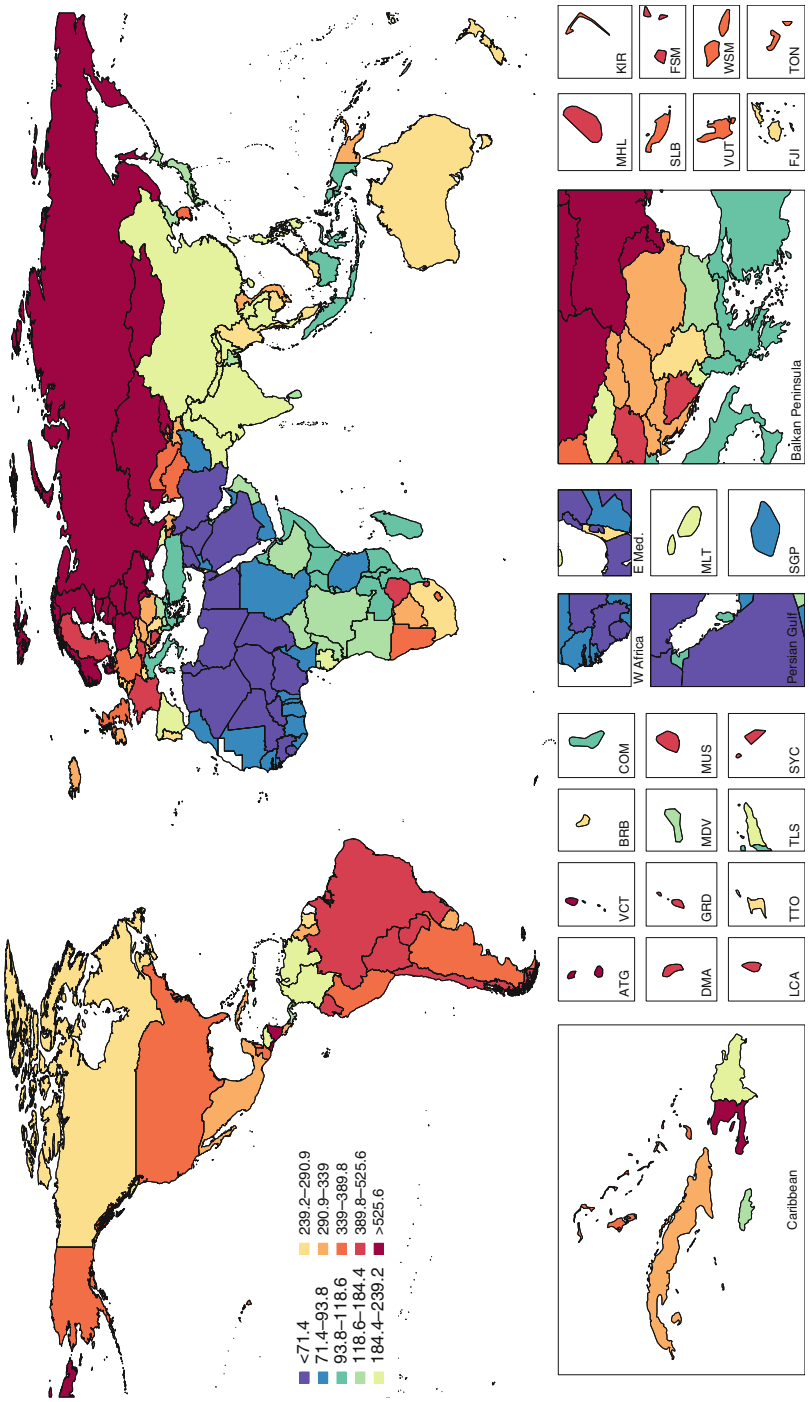

Fig. 4.1 Alcohol use disorders DALYs per 100,000 people, age-standardized, both sexes, 2010

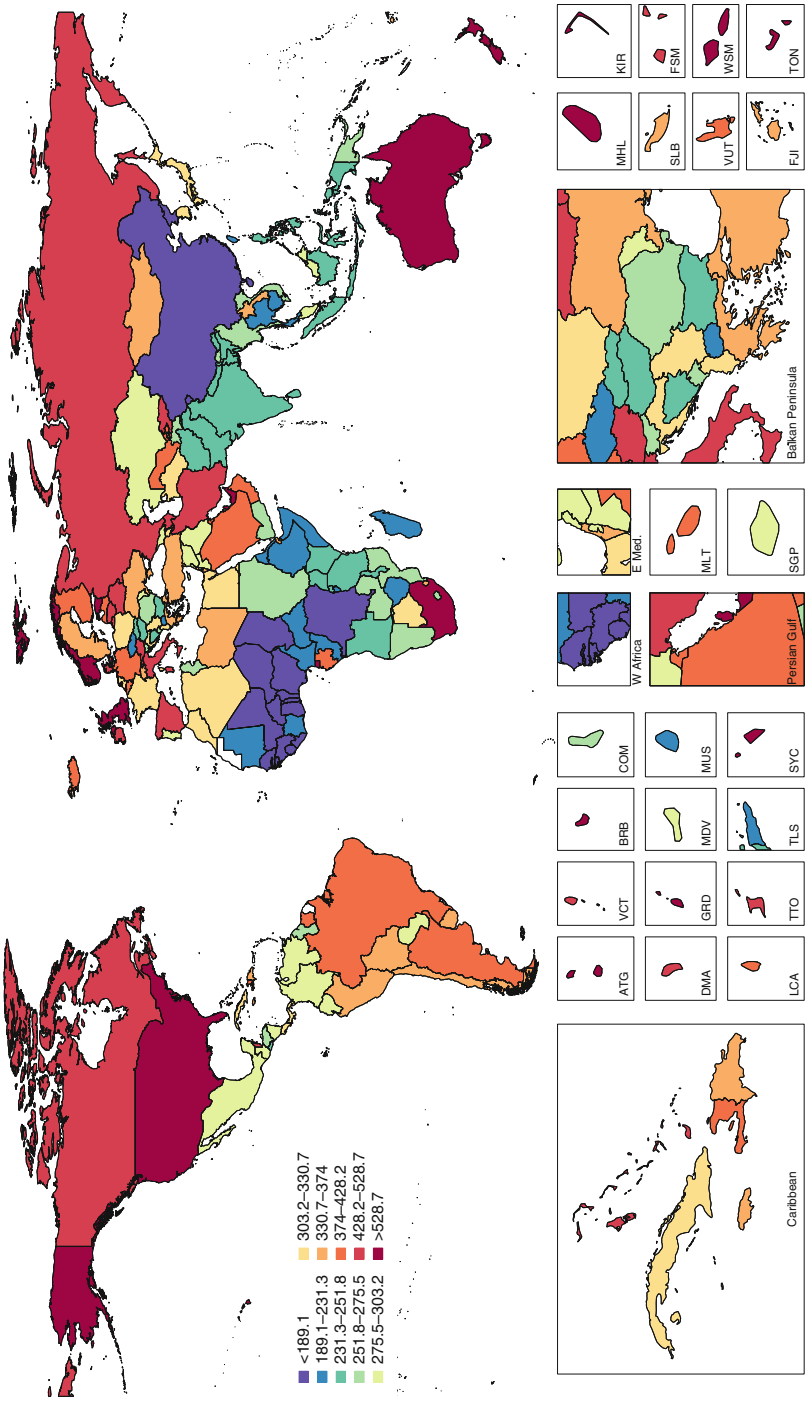

Fig. 4.2 Drug use disorders DALYs per 100,000 people, age-standardized, both sexes, 2010

opioid use disorders and cocaine use disorders were highest in North America (high income) (292 DALYs and 77 DALYs per 100,000 people for opioid and cocaine use disorders, respectively). The burden of amphetamine use disorders was highest in South East Asia (68 DALYs per 100,000 people), for cannabis use disorders it was highest in Australasia (93 DALYs per 100,000 people), and for other drug use disorders it was highest in Southern Sub-Saharan Africa (194 DALYS per 100,000 people). For comparison, the global burden of drug use disorders in 2010 was 291 DALYs per 100,000 people; opioid use disorders were responsible for 133 DALYs per 100,000 people, cocaine use disorders were responsible for 16 DALYs per 100,000 people, amphetamine use disorders were responsible for 38 DALYs per 100,000 people, cannabis use disorders were responsible for 30 DALYs per 100,000 people, and other drug use disorders were responsible for 73 DALYs per 100,000 people.

The burden of alcohol use disorders was much greater in developed countries than in developing countries, with 453 and 211 DALYs per 100,000 people caused by alcohol use disorders in 2010 in developed and in developing countries, respectively. As with the burden caused by alcohol use disorders in 2010, the burden caused by drug use disorders in 2010 was much greater in developed countries than in developing countries, with 545 DALYs per 100,000 people and 253 DALYs per 100,000 people caused by drug use disorders in 2010 in developed and in developing countries, respectively. For opioid use disorders (222 DALYs lost in developed countries per 100,000 people and 113 DALYs lost in developing countries per 100,000 people), cocaine use disorders (34 DALYs lost in developed countries per 100,000 people and 12 DALYs lost in developing countries per 100,000 people), cannabis use disorders (50 DALYs lost in developed countries per 100,000 people and 25 DALYs lost in developing countries per 100,000 people), and other drug use disorders (114 DALYs lost in developed countries per 100,000 people and 64 DALYs lost in developing countries per 100,000 people), the burden was much greater in developed countries compared to developing countries; however, with respect to amphetamine use disorders, the burden was greater in developing countries (39 DALYs per 100,000 people) compared to developed countries (34 DALYs per 100,000 people).

4.2 Transition into Substance Use Disorders

There is a history of use initiation and usually an observable pattern of hazardous use which precede substance use disorders. Generally, these observable trajectories can be approached from either a drug-centered or an individual-centered perspective (Le Moal and Koob 2007); this chapter will focus on the main individual-centered aspects and will not deal with differences between specific substances.

4.2.1 Initiation of Use

The initiation of substance use depends largely on social and environmental factors, such as cultural context, advertising, or peer influence. Worldwide *per capita*

consumption and rates of abstention differ greatly between countries (Degenhardt et al. 2008; Rehm et al. 2009; Shield et al. 2013; Degenhardt and Hall 2012). For instance, lower abstention rates from alcohol consumption are observed in high-income countries and higher abstention rates are observed in North African, Eastern Mediterranean, and South Asian countries (World Health Organization 2011); higher abstention rates are often associated with religious beliefs and with low economic wealth (Shield et al. 2011). Substance use initiation often appears in adolescence, but with some cultural and substance-specific variances (Degenhardt et al. 2008); for instance, in India and in Thailand, even though the age of initiation for alcohol consumption has declined, it remains in the 20s (Gururaj et al. 2011; National Statistics Office 2005). Across substances and cultures, women are less likely to initiate substance use (Degenhardt et al. 2008). Substance availability (Popova et al. 2009; Lipperman-Kreda et al. 2012) and advertising (Smith and Foxcroft 2009; Hanewinkel et al. 2011; Lin et al. 2012) have been shown to influence initiation of use. Beyond these influential cultural factors, the initiation of use is influenced by the individual's social network and close environment. Several studies have shown that social motives, peer or familial substance use, and normative beliefs of close peers influence initiation of substance use across different substances (Kuntsche and Mueller 2012; Galea et al. 2004; Olds et al. 2005).

4.2.2 Transition into Risky Patterns of Use and Substance Use Disorders

While most users maintain a non-risky pattern of use, some individuals will develop hazardous patterns of substance use (Swendsen and Le Moal 2011). In particular, early onset of substance use has been shown to increase the risk of later hazardous substance use across substances (Pitkanen et al. 2005; Adam et al. 2011). With respect to alcohol, recent research indicates that early drunkenness is especially associated with later hazardous patterns of alcohol consumption (Kuntsche et al. 2013). A review identifying the characteristics of people with hazardous alcohol consumption patterns in Europe (Kuntsche et al. 2004) observed that hazardous drinking patterns were more prevalent in males, adolescents, and young adults. Furthermore, the review identified other social and environmental factors, such as the predominant drinking culture, peer influences (see also Borsari and Carey 2001), parental monitoring (see also Danielsson et al. 2011), and concurrent use of other substances. Finally, the motivation for alcohol consumption seems to evolve from social motives and curiosity, predominantly as controlled use, to hazardous consumption patterns motivated by enhancement and coping (Kuntsche et al. 2005).

The factors which influence the transition from hazardous use patterns to substance use disorders are less evident. Impulsivity-related personality traits, such as sensation-seeking or the desire to be uninhibited, influence the transition from controlled use to hazardous use and from hazardous use to the development of substance use disorders (Kotov et al. 2010; Stautz and Cooper 2013). Intraindividual vulnerabilities, such as genetic factors (Le Moal and Koob 2007; Kendler et al. 2007) and comorbid

psychiatric or mental disorders (Swendsen and Le Moal 2011), can be identified as characteristics of individuals who transition to substance use disorders. In particular, high rates of incident substance use disorders have been observed, for people with prior mood, anxiety, and personality disorders (Swendsen et al. 2010).

Almost three decades ago, Khantzian (1985) developed the "self-medication hypothesis" in order to explain the development of addictive disorders where there was a prior background of mental illness or pain; this hypothesis is still discussed today (e.g., Lembke 2012). Stress and stressful and traumatic life events are also important contributors to the development of substance use disorders (Logrip et al. 2012). Adolescents and young adults show an elevated prevalence of substance use disorders in several countries, with higher rates in men (Merikangas and McClair 2012; Khan et al. 2013). There are regions of the world, however, where middle-aged men have the highest prevalence of substance use disorders (e.g., some countries in the European Union – (Rehm et al. 2005), or Russia – (Neufeld and Rehm 2013)).

4.2.3 Conclusion

The onset of substance use is largely influenced by cultural factors and often begins at a young age. It may be assumed that hazardous use precedes the transition to substance use disorders, but scientific evidence is limited in this regard. The majority of studies do not investigate the respective transitions separately, and longitudinal study designs risk missing the phase of hazardous use due to long study intervals. Furthermore, a large number of risk factors seem to exist for transitions to hazardous use and to substance use disorders. Environmental and social factors appear to be more important in the transition to hazardous consumption, whereas genetic risk factors and individual vulnerabilities appear to be more important for the transition from hazardous consumption to substance use disorders (Kendler and Prescott 2006; Tsuang et al. 1998; Vink et al. 2005; Fowler et al. 2007). Social factors play a role in

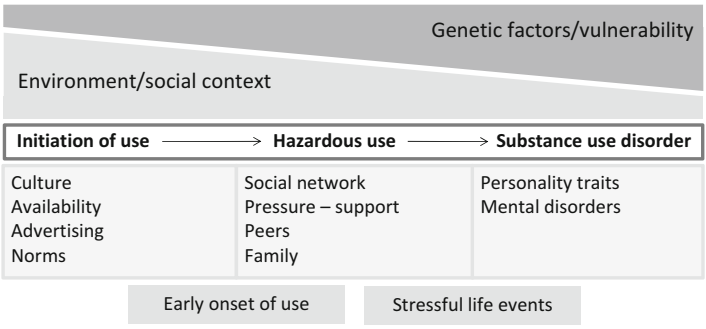

Fig. 4.3 Heuristic model of risk factors for initiation of substance use and transition to substance use disorders

the transition from hazardous consumption to substance use disorders as well, however. For example, during the Vietnam War many United States' soldiers became dependent on heroin. After returning to the United States, the majority of these heroin addictions ceased (Robins 1993; Robins and Slobodyan 2003), but in the minority of cases where the addiction persisted, family history and genetically driven vulnerabilities are considered to have played a major role. The risk factors and their differential influence on initiation and hazardous progression of substance use are summarized in Fig. 4.3.

Appendix

Definitions of scientific terms

Term	Definition
2010 Global Burden of Disease study	The largest systematic effort to describe the global distribution and causes of a wide array of major diseases, injuries, and health risk factors, and a follow-up to the 2004 Global Burden of Disease study
Age-standardized	Rates that have been adjusted to minimize the differences in age composition of a population (used when comparing rates from different populations)
Confidence interval	A range of values where there is a given probability (in this case, 95 %) that the true value (in this case, Disability Adjusted Life Years) is contained within this range of values
Delta	The percentage change in the value of a measure between two conditions (in this case, time)
Disability Adjusted Life Years	A measure of population health loss or burden of disease that takes into account years of life lost due to premature mortality and years of life lost due to disability
Burden of disease	A measure of health loss from diseases, conditions, and injuries as measured by Disability Adjusted Life Years
Incidence	The number of new cases of a disease, condition, or injury during a given period of time for a specified population
Mortality	Death
Prevalence	The number of people with a given disease, condition, or injury at any point during a given period of time (e.g., annual, lifetime, period, or point)
Systematic review	The application of search and evaluation strategies that limit bias in the assembly, critical appraisal, and synthesis of studies that are relevant to a topic
Years of life lost due to premature mortality	A measure of health loss due to premature mortality, which is calculated as an estimate of the number of years people would have lived if they had not died prematurely
Years of life lost due to disability	A measure of health loss due to disability, which was calculated in the 2010 global burden of disease study as the point prevalence of a disease, condition, or injury multiplied by a corresponding disability weight (a measure of health loss caused by a disease condition compared to total health loss (i.e., death))

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Changing Patterns of Drug Use in Georgia: A Case Vignette

5

Irma Kirtadze and David Otiashvili

Contents

Abstract

In Georgia rapid economic, political, and social changes since gaining independence from the Soviet Union in 1991 and relaxation of state control have been accompanied by the scale of the illicit drug market. Drug use has become a serious public health and social issue. Heroine and buprenorphine injection epidemics of late 1990s–early 2000s were followed by the widespread abuse of home-produced injection preparations. Switching to new drugs in many instances was associated with increased risk of blood-borne infections and additional harms, such as serious neurological and psychiatric complications. Restrictive drug policy and limiting access to particular drugs were seen as solutions to country's drug problem. In addition, the system of addiction treatment was largely unprepared to provide adequate response to the changing drug use trends and often failed to meet the needs of the patients. Health-care providers might often need to engage in policy dialogue and advocate for relevant systemic reforms in order to ensure that policies, program planning, and resource allocations are meaningful, adequate, and responsive to the ever-changing needs of people affected by substance use and dependence.

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5.1 Introduction

Georgia is a parlimentary republic located in the South Caucasus. The country consists of 11 regions with overall population of 4.5 million. Tbilisi, the capital of Georgia, contains the largest proportion of the population with 1,253,000 living there. Two regions of the country, Abkhazia and South Ossetia, are cut off from the rest of Georgia. These Georgian territories are sequestered as a result of internal conflicts since the early 1990s and subsequent de facto Russian Federation occupation in 2008. Approximately 288,000 persons are internally displaced in Georgia. The state language is Georgian and the main religion is Orthodox Christianity.

Georgia is a wine-producing country and consumption of alcohol is traditionally high. With almost 80 % of general population having ever used alcohol, 63.6 % admitted its last month use. Tobacco smoking was reported by 30.3 % of respondents with dramatic gender difference, 55.5 % for males vs. 4.8 % for females (Sturua et al. 2010). Marijuana is the most widely used illicit drug; however, prevalence data for general population is not available. In a recent Youth Behavioral Surveillance Survey, slightly over 10 % of students aged 15–24 admitted lifetime use of marijuana, and the highest prevalence was reported for males aged 18–24, 24 % (Dershem et al. 2012).

Georgia has experienced rapid economic, political, and social changes since gaining independence from the Soviet Union in 1991. With the relaxation of political, social, and trade control, the scale of the illicit drug market has increased and drug use has become more common. Socioeconomic transition, civil war, and ethnic conflicts, all contributed to increased illicit drug markets and drug use. In relation with injection use of illicit substances, the last two decades have been characterized by dynamic changes in drug use trends and patterns in the country. Traditional raw opium was pushed out of the drug scene by rapid introduction of heroin in mid-1990s. Heroin was later partially replaced by buprenorphine in the form of Subutex® tablets (Javakhishvili et al. 2006). Buprenorphine, which was not registered in Georgian health system until 2010, was illegally smuggled from Western Europe and occupied significant share of illicit drug market for few years. Subutex® was reported as the primary drug of dependence for 40 % of patients admitted to inpatient treatment in 2005 (Javakhishvili et al. 2006).

Since 2002 there has been a marked increase in injection use of homemade amphetamine-type stimulants (ATS) prepared from cold and cough medicines containing pseudoephedrine or phenylpropanolamine that are easily available from pharmacies without a prescription (Javakhishvili and Sturua 2009). The final injectable product of the preparation contains amphetamine and methamphetamine (street name "vint": a long-acting stimulant prepared through the reduction of pseudoephedrine) or methcathinone (street name "jeff" or "boltushka": a short-acting stimulant prepared through the oxidation of pseudoephedrine). Since 2010, the range of readily accessible homemade injectable drugs was enlarged by the so-called krokodil (desomorphine), produced from the pharmaceutical drugs containing codeine (Javakhishvili et al. 2012).

In 2011–2012 desomorphine (krokodil) and homemade ATS (vint and jeff) were leading drugs for injection in the country with significant portion of injectors using both preparations. Data from the database of Georgian Harm Reduction Network (largest provider of low-threshold services to people who inject drugs in Georgia) show that in 2012, the last month prevalence of injection use of krokodil was 42 % and the prevalence of stimulants injection was 37.5 % in a sample of 1,092 participants (40 females) of needle/syringe programs. For comparison, last month prevalence of heroin, opium, and buprenorphine injection were 31 %, 10 %, and 9 %, respectively (Georgian Harm Reduction Network 2012).

To provide a full picture of the ever-changing drugs scene, it is important to discuss the abuse of other products and over-the-counter medications that were popular for shorter periods of time and/or were characteristic to particular geographic areas of the country. In 2003 Georgia experienced an explosive abuse of a preparation produced from poppy seeds that are normally used as an ingredient for different food (confectionery manufacturing). In 2005–2008 injection use of antidepressant tianeptin (Coaxil®) was widely reported from different regions, in particular West Georgia (Javakhishvili and Sturua 2009). Finally, in 2010–2011 widespread oral consumption of anticonvulsant pregabalin (Lyrica®) was observed throughout the country.

Common features of Georgian drug scene can be described as follows: major drugs are used exclusively intravenously (no sniffing, smoking, or inhaling); daily doses of Georgian injectors are comparatively low; in most of the cases opioids are combined with benzodiazepines and other sedatives (including antihistamines with sedative effect); unstructured polydrug use is common. In the Georgian setting, benzodiazepines and other sedatives are added to opioids in order to increase the potency and duration of effect of a small dose of narcotic. In addition to the concurrent use of sedatives, the use of homemade stimulants is common. Even if polydrug use is a well-known phenomenon in the region and is confirmed by other authors (Booth et al. 2008; Kruse et al. 2009), Georgian studies indicate a scenario of even more chaotic drug use. Among other factors, the reasons for unsystematic polydrug use (mixing together opioids with other sedatives and with pseudoephedrine-based stimulants at the same time) might be the fluctuating availability of particular substances, the high price of all illegal drugs on the Georgian black market compared to local income levels, and the users' attempts to combine different drugs in order to increase the euphoric effects, potency, and duration of effect of the preparation.

Development in substance use patterns obviously depends on a complex set of contributing factors and socioeconomic context in the country. Not surprisingly, in many cases drug use trends in Georgia were shaped by policy response, legal environment, and law enforcement practice implemented at particular periods of time. It has been argued that the relatively long-lasting effect of buprenorphine injection (compared to heroin or opium) and less obvious external signs of intoxication contributed to its popularity in the Georgian drug-using setting (Otiashvili et al. 2010). Since the mid-2000s, there has been a dramatic increase in police activity aimed at random street searches and (urine) testing of people for drugs,

which, in the event of a drug being found or a drug-positive urine toxicology result, leads to harsh penalties (Otiashvili et al. 2008). Thus, buprenorphine might have attracted drug users because of its moderate clinically visible signs after its intake. Furthermore, for several years the police did not check suspects for the presence of buprenorphine in their urine, but rather concentrated on the traditional opium and heroin. This lack of detectability could in fact have added to the "attractiveness" of buprenorphine and other drugs for local drug users. Similarly, a pattern of increased homemade stimulant and homemade opioid injection followed the reduced availability of heroin and other "traditional" opioids. This was partially preconditioned by the fact that police traditionally targeted heroin and opioid markets and users switched to alternatives, which did not necessarily require involvement with illegal drug market. Again, for initial period of time, neither vint and jeff nor krokodil was properly detected through urine toxicology testing. Importantly, these alternatives were remarkably cheaper, $5–7 per single dose of vint, jeff, or krokodil, compared to $50–100 per single dose of heroine or buprenorphine.

Abuse of poppy seeds, tianeptin and pregabalin provide an additional proof of the concept described above. In all those instances, the major reason for experimenting with new preparations was drug users' attempt to self-medicate and substitute their traditional drug of abuse. Importantly, neither tianeptin nor pregabalin was identifiable through rapid urine testing, and the single dose of either preparation costs less than $10. As a policy response, all these medications, including poppy seeds, were rescheduled and put under the strictest control regime, which ultimately dramatically limited access to these preparations. Not surprisingly, drug users just went on with exploring new options.

Switching to new drugs in many instances was associated with increased risk of blood-borne infections (high frequency of injection, group character of use, sharing of paraphernalia, and risky sexual behavior) and additional harms, such as serious neurological and psychiatric complications (due to toxicity and/or insolubility of chemical ingredients used for processing the preparations) (Sikk et al. 2007). Krokodil, which received its name due to association with "crocodile eating your flesh," is probably one of the most toxic preparations injected in Georgia. Apart from quickly progressing severe neurological impairments, its use causes skin irritation and soft tissue damage. Reports provided by harm reduction and drug treatment facilities suggest that due to the fluctuating potency of the preparation, depending on the process of its refinement, krokodil injectors are at increased risk for overdoses. It is indicative that harm reduction programs in Georgia report an increased demand for naloxone.

In a country with an HIV epidemic driven by injecting drug use (56 % cumulative HIV cases attributed to IDU route (Chikovani et al. 2011b)), risks associated with the use of particular substances are of special interest. Common unsafe injection behavior among Georgian IDUs known to be sharing a cooker and dividing solution using one syringe (Chikovani et al. 2011a). In-depth analysis of drug preparation and drug division processes helps provide a meaningful explanation for these particular types of risk behavior. Buprenorphine (Subutex®) injection in Georgian setting occurs as a rule in a group of three to four people. They dissolve

one 8 mg tablet in water and then, using a large-volume syringe, divide the solution by front or back loading into smaller individual syringes (Otiashvili et al. 2010). Home preparation of both amphetamine-type stimulants (vint and jeff) and opioids (krokodil) involves using common cooker to process ingredients through often-complicated chemical refinement and using large-volume syringe to divide the final product into smaller syringes for injection (front and back loading). In both cases drug preparation is a group activity with often-predetermined division of roles and contributions (money, ingredients, space for production). Injecting stimulants from preloaded (by someone else) syringes was also reported.

5.2 Georgia's Management Features

5.2.1 Treatment Response

To a large extent, the development of addiction treatment in Georgia has been shaped by the school of Soviet "narcology" that operated within a highly centralized and closely regulated vertical health-care system. A focus on heavy medicalization, an emphasis on administrative duties, rather than positioning themselves as care givers, and few incentives to seek major changes in the field, all have historically been characteristics of Soviet narcologists (Elovich and Drucker 2008; Latypov 2011). It was in the mid-1990s when Georgian doctors finally had an opportunity to communicate with their western counterparts, to get exposed to the notion of evidence-based medicine and to start introducing novel approaches into their practice. One of the turning points in this regard was approval of agonist medication treatment and its inclusion in the law in 2002, and the role of professional community in this process was critical. The methadone program was then launched in 2005, and buprenorphine was introduced as agonist treatment in 2010. Remarkable scale-up of agonist treatment and state support for it probably represents major achievement in a history of Georgian addiction treatment. In 2011 more than 2,300 patients received agonist medication treatment in 17 sites throughout the country (Javakhishvili et al. 2012).

It should be noted that apart from positive development with regard to agonist medication treatment, the system of addiction treatment, its institutional infrastructure, and state support were all static for the most part of the time in the last decade, and no adequate response to the changing drug use trends and needs of the clients was provided. Until 2009 no state or municipal financial support for treatment was available, and patients were paying cost of treatment out of their pockets, which significantly limited accessibility of treatment. As of 2012, no system of comprehensive treatment approach has been implemented that would utilize treatment planning, case management, and notion of continuum of care. Given the lack of systemic response, it was the doctor-narcologist who was responsible for overcoming the challenges the system was facing and exploring options available at-hand. Too often these options were very limited, in particular in relation to abuse of substances that were not commonly used in the developed world and were not

described in international literature: poppy seeds, tianeptin, buprenorphine, homemade stimulants, and krokodil.

Currently, homemade stimulants use and poly-substance use represent major challenge for the Georgian treatment system with no formalized approach adapted for any of these conditions. The systems have been largely unprepared for the ATS epidemic as service providers were focusing on opioid users and were not ready to address increased demand for managing stimulant and polydrug abuse. Another major system challenge is an absence of gender-specific services; women constitute less that 2 % of clients of drug treatment and harm reduction services. It has been suggested that both sociocultural and structural barriers impede the demand for and access to substance abuse treatment for drug-using women in Georgia (Kirtadze et al. 2013). The role of policy makers, service providers, and clinicians in removing the structural and cultural barriers is critical.

5.2.2 Policy Implications

Limiting access to particular drugs, massive searches, and arrests of drug users were seen as solutions to Georgia's drug problem. Immediate results of this approach were obvious; streets became free of people under the influence and signs of drug-related activities diminished. Thousands of drug users also ended up in prisons. These actions have had multiple, radiating, unintended consequences. For example, these actions resulted in drug users switching to more available, cheap, and largely harmful and toxic home-produced preparations and exercising more life-risky patterns of use. No evidence of reduced prevalence of drug use is available. As of 2010, there are an estimated 40,000 regular injection drug users in Georgia. Thus, the problem has not been reduced. In fact, the rate of the problem in drug use is approximately 2.5 times higher than the average European estimates (Sirbiladze 2010). Within a 4-year period, the prison population has increased fourfold (from 6,000 to 24,000), and Georgia in 2011 rated sixth in the world by per capita number of prisoners (International Centre for Prison Studies 2011). This high incarceration rate has placed economic and social burden on the families of incarcerated drug users (e.g., separating mothers and fathers from children, leaving families without economic means of support both during the incarceration and after release when drug users with incarceration histories face extreme difficulties in obtaining a job). Heavy emphasis on law enforcement measures has resulted in a disproportionate allocation of resources to programs aiming to provide health and social care to people with substance use-related problems. Countrywide, only about 6 % of those who are in need receive any kind of drug dependence treatment (2,520 out of 40,000 in 2011) (Javakhishvili et al. 2012).

Hopefully, as of the start of 2013, major policy reform was discussed; Drug Policy Coordination Council has been established and drug-related legislative initiatives have been reviewed in the Parliament. Importantly, this process has been inclusive and transparent enough and has engaged all major stakeholders: policy-makers, service providers, field experts, and representatives of affected groups. It is hoped

that newly elected government officials will be committed to recalibrate current drug policy regime and will build a system in which tolerance and care for those in need, effectiveness of interventions, and evidence-driven decision-making will be prioritized.

5.3 Conclusion

In conclusion, it is obvious that health-care professionals working in addiction treatment would benefit from gaining knowledge, skills, and, most importantly, motivation to create an emotionally and physically safe treatment environment, improve its quality, and introduce structural and procedural changes that would make treatment both attractive and accessible. Medical personnel play a critical role in exploring and utilizing approaches that are based on the best available scientific evidence and that respond to the needs of those who would ultimately benefit from it. Importantly, Georgian experience shows that clinicians might often need to engage in policy dialogue and advocate for relevant systemic reforms in order to ensure that policies, program planning, and resource allocations are meaningful, adequate, and responsive to the ever-changing needs of people affected by substance use and dependence in their respective country or region.

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Social Aspects of Addiction and Environmental Strategies

6

Joseph Westermeyer

Contents

This article reflects the opinions of the author only and not those of the Minneapolis VE Health Care Center or the University of Minnesota.

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Abstract

Social-environmental factors serve two functions in addiction care, i.e., (Bean, Zinberg (eds) (1981) Dynamic approaches to the understanding and treatment of alcoholism. New York, The Free Press) for diagnosis, assessing the *social-environmental nature and severity* of the addiction and (Berne (1964) Games people play – the basic handbook of transactional analysis. New York, Ballantine Books) for treatment, identifying *social-environmental obstacles and resources* to recovery. In clinical settings, addicted persons may try to maintain addiction by eliciting *rescuing* or *enabling* behavior from clinicians and other parental figures; the antidote consists of adult-adult transactions aimed at *recovery*. Depending on the clinical context and phase of recovery, clinicians can choose a variety of roles vis-à-vis the addicted patient, i.e., impersonal or mechanistic *I-it* for early detoxification, formal *I-You* for diagnosis and treatment planning, and personal *I-thou* during later recovery. Ultimately, the recovering addict must achieve trust within himself/herself and regain the trust of others, through acquiring personal and social integrity. Two available social entities consist of mutual-help groups (e.g., Alcoholics Anonymous, Narcotics Anonymous) and the family. These two resources can gird the addicts in re-creating a supportive, functional *intimate social network* (ISN) – a core foundation for happy and healthy living. Clinicians' understanding of the ISN structures and functions provide a potent means for coaching addicts in recovery. In addition to clinicians, families, and mutual-help groups, communities, governments, and society at large can design environments that facilitate relapse or favor recovery. *Social-environmental obstacles* include a high prevalence of addiction and local profiteer-enablers who prey upon addicts. *Social-environmental resources* include clear norms regarding substance use, availability of timely treatment, and implementing prevention strategies. Coordinated international action can bolster local social-environmental initiatives.

6.1 Introduction

Much clinical research on addiction emphasizes the individual addict in isolation from other people. Examples include the addicted person's genes, responses to addictive substances, course of addiction over time, psychopathology, medical and psychiatric comorbidity, response to pharmacotherapies and psychotherapies, individual avenues to recovery, and causes of death. These individual-focused topics remain important and relevant. As clinicians, we often encounter the addicted person in isolation. Our professional ethics bind us to the individual patient, and various legal dictums (such as privacy and confidentiality) may seem to exclude others from the clinician-patient relationship, or at least render it difficult to include them.

This section focuses on addicted persons in social and environmental contexts. "Social" refers here broadly to anyone outside of the individual addicted person, from one other person (including clinicians) to various larger groups. These larger groups may include the family, the drinking or drugging group, the intimate

social network, the community, government, and various sociocultural and nongovernmental groups. "Environmental" incorporates all outside forces, events, and objects that act on or affect a person. The individual's relationship with the environment is dynamic: he/she interacts with the environment, is affected by the environment, and can also act on, influence, or change the environment. Related topics covered in other sections of this volume consist of Social Therapies and Treatment Settings (Sect. 5) and Systems, Approaches, Public Policies, Evaluation, and Outcome of Treatment (Sect. 6). Information provided here provides relevant background information for these subsequent sections.

6.2 The Social Context

6.2.1 The Addicted Person in Social Context

Interpersonal Psychodynamics in Addiction. The personal characteristics of the addicted person impinge on transactions with other individuals, as well as with groups. Perhaps the most common psychodynamics appearing over time in the addiction process are denial and projection. From the addicted person's perspective, these are inherently social explanations for the addiction. In brief, the addicted person initially denies that he/she is responsible for the excessive use of psychoactive substances or its consequences. Instead they blame another person or group for the addiction (e.g., family, employer, the world at large). This blaming of another comprises projection, the attribution onto others that they have produced the addicted person's failures and problems.

Some element of truth may underlie the addicted person's blaming of others, whether for the family's passing on genes that produce vulnerability, or teaching values or behaviors that foster excessive psychoactive use, or failure to intervene early upon the appearance of pathogenic psychoactive use. Despite these threads of reality, the belief that others have produced one's own behavioral problems can seriously impede one's efforts at recovery. The addicted person must take responsibility for his or her own recovery in order to work free of addiction. Blaming other persons ("my alcoholic father") or groups ("the racists," "the government") may offer some transient solace early on, but poses a profound obstacle to ultimate recovery.

Therein lies a paradox for both the clinician and the recovering addict. On one hand, the clinician's treatment and the addict's recovery converge on the notion that the addict must take responsibility for his or her own individual recovery. By the same token, clinicians' attention and recovering addicts' linkages to interpersonal and social-environmental factors encompass key steps to successful outcomes. This complex notion – personal responsibility bridging to social reintegration – does not surface suddenly to the addict's awareness. Rather it evolves gradually, growing out of experience as well as knowledge. Probably, it is best that it develops thus, since sudden awareness of one's responsibilities for recovery and the momentous tasks and time required for social reintegration could overwhelm the struggling patient, precipitating a return to addiction or even respite seeking in suicide (Bean and Zinberg 1981).

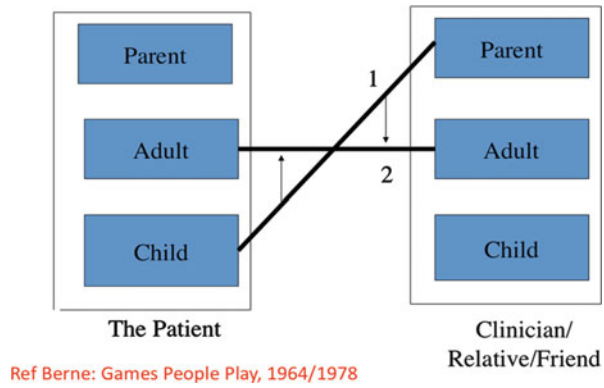

Fig. 6.1 Eric Berne's interpersonal relationship model (Transactional analysis)

6.2.2 Using Interpersonal Psychodynamics in Treatment

The actions of addicted persons in relation to others can be described using the social roles of "parent," "adult," and "child," as shown in Fig. 6.1. These parent-adult-child terms correlate loosely with the psychoanalytic terms "superego," "ego," and "id."

Addicted people sometimes assume the "child" role in relation to parental figures, such as clinicians and judges. This interpersonal strategy aims at eliciting addiction-perpetuating succor from the other person's "parent." As applied to addiction, a rescuing or enabling interaction may ensue (Berne 1964).

Rescuing entails the "parental-helper" saving the "childish-addict" from the consequences of his or her behavior. For example, a judge may let the addicted criminal off without punishment, or a clinician may repeatedly treat the addict's damaged health without attending to the addictive disorder that is causing the illnesses. *Enabling* implies that the parental figure provides resources that permit the addicted person to have the time and/or resources to continue an addiction-focused lifestyle. For example, a family member or friend may provide the addicted person with money, shelter, food, or transportation to purchase psychoactive substances and avoid social responsibilities. Both rescuing and enabling are depicted by the child-parent relationship depicted as "1" in Fig. 6.1 (Berne 1961).

Recovery requires the addicted person to act in "adult-to-adult" relationships; see relationship "2" in Fig. 6.1. This transition from child-parent to adult-adult transactions may not be easily accomplished. Clinicians can assist recovering patients and their rescuers-enablers with this often-difficult change as follows:

- Instruction regarding interpersonal roles, choices, and dynamics
- Feedback regarding "childlike" behaviors of the addicted person's part (e.g., missing or coming late to appointments, requesting prescriptions for addictive medications, requesting treatment while undermining its beneficial effects by continued addiction)
- Clinician's opting out of parental behaviors that promulgate addiction (e.g., prescribing addictive substances, providing written excuses for irresponsible or illegal behavior, undertaking or persisting in treatments rendered ineffective by addiction).

Using the paradigm described in Fig. 6.1, recreation with others tends to occur on a "child-to-child" transactional level. As recovery proceeds, the ability to recreate without recourse to alcohol-drug use poses an obstacle for many recovering persons. If their former recreation did not depend on substance use, they may simply return to their former pastimes, hobbies, or avocations. However, if their former recreation occurred in a context of substance use, they need to seek new opportunities free of substance use. Mutual-help associations and recovering groups realize this dilemma and often create recreational activities for times that favor excessive use (e.g., New Year celebrations). Clinicians should aid in this crucial aspect of recovery, since the absence of play and social "time out" from daily responsibilities can undermine an otherwise well-founded recovery.

In certain respects, clinicians can behave appropriately toward recovering patients in the "parent" role. Examples include making and conveying diagnoses, providing counsel, or prescribing medications for detoxification, craving, maintenance, or comorbid disorders. Although aimed at being therapeutic, this approach may engender childlike responses from the recovering patient (e.g., resentment, sociopathic "acting out" of negative attitudes toward the clinician or the treatment process, return to addiction). Several alternatives can aid in reducing these "parental" impediments as follows:

- Working with co-therapists who can assume a more egalitarian approach to the patient
- Assuming more the role of a "coach-trainee" than a "doctor-patient"
- Providing choices between alternative therapies, so that the patient is engaged as a codirector of treatment
- Educating the patient to the pros and cons of alternative approaches and allowing some time interval for the patient to consider the alternatives, seek other information, or obtain counsel from others before making a decision or requesting the patient to make a commitment

6.2.3 Impersonal, Formal, and Personal-Informal Relationships

Addicted persons, as well as their clinicians and other members of their social networks, can behave on several operational levels vis-à-vis the other. For purposes here, these three types of interpersonal relationships are used synonymously with I-focused typologies that have evolved over the last several decades (Farber 1956):

- Impersonal = I-it relationship
- Formal = I-you relationship
- Personal = I-thou relationship

The "I" in an I-it relationship relates to the other person in a mechanistic, largely I-centered fashion. For example, an addicted person seeking drugs from a clinician has an unshared goal with the clinician (i.e., obtaining addictive medications) as opposed to a shared goal (i.e., health seeking). Such patients may experience problems in changing their attitude toward clinicians from "naïve target" to "trusted helper." We as clinicians may act in I-it roles with unconscious patients

(e.g., administering an antagonist medication to an overdosed patient), selecting an appropriate medication for a withdrawal regimen or – in selected respects – treating a legally incarcerated or committed patient. Such impersonal or authoritarian roles also occur in other social interactions involving addicted persons (e.g., discharging an addicted employee or divorcing an addicted spouse). This type of relationship is not so much social as asocial or mechanical in its salient features. Although interactions on this level can be life saving and caring, they also carry the risk of becoming dehumanized or uncaring. Such relationship can also occur on a larger social plane, with administrators or societal leaders relating to addicted persons in a demeaning or solely economic and legal fashion (Ticho and Wnnicott 1974).

"I" in the formal I-You relationship functions in a dyadic but role-driven fashion with the other person. The relationship operates within formal social rules and cultural expectations. For example, the addicted person in a formal patient role would relate to the clinician by expressing their health-related problems and concerns forthrightly, answering the clinicians queries as they are best able, and complying with treatment recommendations. Conversely, the clinician would conduct a competent evaluation, render a reasoned assessment or diagnosis, and provide a prognosis and treatment recommendations supported by the findings. Traditions, customs, personal experience, education, professional ethics, regulations, and laws prescribe the parameters governing these formal roles. For example, social workers may act the role of housing providers for addicted persons, or police may act the role of security enforcers. As a result of negative relationships with various other people in their formal roles, addicted people can have difficulty maintaining functional relationships on this level during early recovery.

I-thou relationships include more egalitarianism and greater informality. They inevitably involve such attributes as mutual trust, commitment, and benefit. For example, the patient may ask the clinician which therapeutic alternative seems the most likely to proceed or thank the clinician after an appointment. Or the clinician may congratulate the patient for achieving a therapeutic risk or reaching a recovery milestone. These informal communications do not inactivate the formal social frame that provides the necessary boundaries to the therapeutic relationship, but they can greatly facilitate and humanize the therapeutic encounter.

The nature of the "I" relationship can change over time. For example, the clinician may take the I-it role early in a medical crisis; then change to I-You transactions during later assessment, treatment and early recovery; and finally adjust care to encompass I-thou elements during the later months and years of recovery. Slips or relapses may compel a return to an earlier mode of relating.

6.2.4 Recapturing Social Integrity

By the time they seek treatment, many addicted people can no longer rely on themselves. Clinicians hear statements like "I can no longer trust myself" or "I lie so much that I don't even know what is the truth anymore" or "I can't make even the simplest promise or commitment." Re-acquiring integrity starts with the self. To regain

integrity, addicts need to work at becoming "one" again. That is, they must have one truth, one set of values. Such constancy is difficult even for nonaddicted persons, since the variety of roles played by any one person varies so greatly. Each of us possesses slightly different personas in our relationships with parents, offspring, spouse, supervisors, co-workers, friends, old buddies from childhood, and clients. These personas if extremely diverse can pull the recovering person away from an evolving core "one-ness," or integrity, toward duplicity and relapse (Sutker et al. 1980).

Over time many people with addictive disorders lose the trust of other people. Stated differently, addicts tend to lose their trustworthiness. Without mutual trust, people are unwilling to live with addicted persons, own material goods in common with them, or exchange mutual obligations. In the absence of such commitments, the addicted person is apt to become increasingly isolated. For a time, wealth may compensate for mutual obligations, posing a greater risk for the wealthy who can hire to people to provide social support. Unfortunately, using wealth to compensate for social isolation can delay recovery efforts. To establish trust, the recovering persons must be honest, truthful, reliable, and morally upright.

Regaining the trust of others presents one of the greatest long-term challenges to the recovering addict. Depending on the duration and depth of past failures, it may take many months to years before former relatives, friends, and others can again trust the recovering addict. With some regular opportunities to regain trust, the recovering person may experience some moderate trust building within a year. Deep trust may take longer. Clinicians can support and guide the recovering person in this quest. Many recovering people expect others to impart trust after one episode, or within a week or two of abstinence. Such disappointments can reignite addiction if the patient is not prepared for it. Once prepared for the long haul, however, most recovering people can launch into the quest of regaining integrity (Westermeyer and Walzer 1975).

Perhaps one of the advantages of becoming again an integrated, trustworthy person is the paucity of people in the networks of many people early in recovery. Since they have lost so many supporters, they can start anew rebuilding on a small number of relationships. Starting simply with only a few relationships eases the task of achieving integrity.

6.3 The Addicted Person's Family

The Addicted Family. In most societies, more than half of addicted persons grew up in a family with an addicted parent. Some addicts even have two parents with an addictive disorder. Or neither parent may be addicted, but siblings, grandparents, uncles, aunts, or cousins may be addicted (Galanter 1993).

Coming from an addicted family can produce a myriad of hurdles. Addiction tends to start earlier in such circumstances. Childhood may have been fraught with stress and conflict, if the parent or parents had not recovered earlier. Role models for later adulthood, marriage, and parenting may be absent or flawed (ElGuebaly et al. 1990; Westermeyer et al. 2001).

By the same token, having an addicted family background can also impart certain advantages. Relatives may recognize the signs of addiction early on, due to their familiarity with it. Especially if familiar with recovery, they may support the addicted relative in recovery-oriented endeavors. Those seeking out recovery-oriented mutual-help groups may come from addiction-afflicted families (Westermeyer et al. 2001). In some countries, mutual-help groups for the adult children of addicts have formed.

6.3.1 Recovery Within the Family

For addicted adolescents and young adults, family therapy can be a highly effective intervention. The same is true of couple's therapy in which one partner is addicted. A key to either alternative lies in seeking a therapist familiar with addiction, recovery, and the treatment of addicted families and couples (Coviello et al. 2004).

If both members of a couple are addicted at the same time, concurrent recoveries occur only rarely. Since recoveries tend to be unique in certain respects and occur unevenly over time, partners seldom recover in the same fashion along the same time frame. This discrepancy wears on the relationship, so that maintaining the blighted relationship while trying to recover becomes nigh unmanageable. A more viable alternative may lie in recovering separately and then deciding whether the two recovered-evolved personas can create a new sobriety-based life together (O'Farrell and Cowles 1989).

Recovered persons, when single, often meet and court other recovered persons. This common, often vexing-yet-rewarding experience can serve as strong groundwork for a successful partnership. Each member shares concepts, jargon terms, and perhaps common recreations and social affiliations with the other. Plus they understand deeply the torments of loss and loneliness, and they share the long, hard trek from addiction through recovery to wellness.

6.4 The Intimate Social Network in Addiction and Recovery

6.4.1 Intimate Social Networks (ISNs)

Several typologies exist for conceptualizing "social networks," such as number of confidants or people contacted in the last week. The one utilized here developed from the work of a psychiatrist who had trained in social science (Pattison 1977). In this format, the individual is asked to name the people who are the most important to them in their current lives. Most adolescents and adults who are functioning at a reasonably comfortable level report 20–30 people, who fall naturally into four or five groups (e.g., people living together, a group of relatives living elsewhere, friends, co-workers, people who share a common interest or pastime); see Fig. 6.2. This small group differs qualitatively from the much larger number of people whom any one individual knows and can name (usually on the order of several

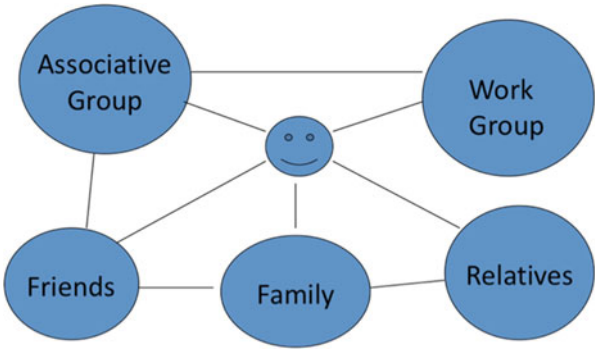

Fig. 6.2 Normal social network n = 20–30, 4–5 groups, reciprocal, 80 % connected, stable over time

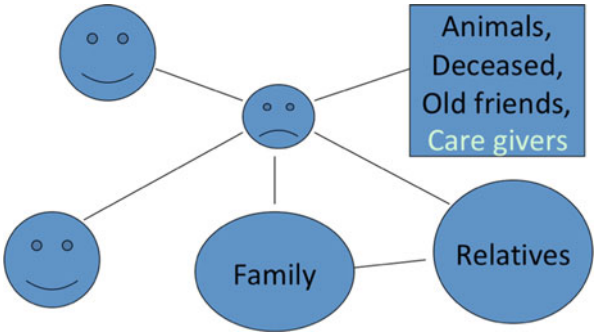

Fig. 6.3 Outpatient social network N = 10–19, 2–3 groups, partially reciprocal, 60 % connected

hundred to a few thousand people). Among adults, the relationships are reciprocal, so that members contribute to or help one another as well as the corporate group in some fashion (e.g., exchanging goods or services, providing interpersonal help or support, meeting common goals). Membership in any one group within the ISN often requires getting along with several people. In this fashion, a person may transcend conflict with any one or a few members of the group in order to retain access to valued members of the group and keep the group intact. Such networks tend to persist over time. Any one person in the proband's network knows about 80 % of the people in the total network (i.e., connectedness = 80 %).

People who seek outpatient mental health services tend to have at least ten, but less than 20 people in their ISN (Westermeyer and Neider 1988); see Fig. 6.3. The network members often fall into two or three groups plus an additional number of one-to-one relationships; see Table 3. These one-to-one relationships may include a recent friend, lover, or someone who provides service or care (e.g., a therapist, clergy, bar tender, barber, or hairdresser). The one-to-one relationships may be more recent as well as vulnerable to change or dissolution over time. At times they report ISN members as being pets, deceased friends or relatives, or close friends from years or decades earlier. Connectedness is around 60 %. These people are typically discomforted, even miserable, but they are functional in one or more capacities, such as working, parenting, or going to school. Among adults, their

relationships tend toward reciprocity although asymmetric relationships may occur in the event of enabling or rescuing relationships (see above). Their entire network may consist of other addicted people (Dumont 1967).

People who are disabled tend to have less than ten members in their ISNs. The members of this group tend to know one another through their supportive roles vis-à-vis the proband. For example, the proband's parent, social worker, and landlord may all know one another as a result of previous experiences with the proband. Connectedness is often 100 %. People in this group tend to have asymmetric or nonreciprocal relationships, since they may not have the resources or skills to reciprocate.

Severely ill people can come to distrust or alienate others to the point that they report no one in their current ISN. They may be homeless and paranoid, surviving on their ability to obtain food, shelter, clothing, and other necessities from the environment. Many, but not all, people in this group have been addicted in the past or remain addicted. Most require psychiatric services, but many can recover over a period of months and years with support.

6.4.2 The ISN in Addiction and Recovery

Actively employed addicts living with family can have social networks that resemble normal networks with one exception: as many as half of the network is comprised of other addicted people (Favazza and Thompson 1984). In order to pursue recovery, they must abandon and then replace the addicted people with whom they are affiliated. This precipitates loss, engenders grieving, and can both help and hinder the adjustment to sobriety.

Most people presenting for addiction treatment have the "discomforted" network, with 10–19 people, 2–3 groups, and one or more individual relationships (with minimal connectedness to the rest of the network). In achieving a comfortable, balanced life and recovery, they usually rebuild their network backup to 20–30 people and four to five groups over a period of years – a much longer period than that needed by people who must rebuild their ISNs after relocating for work or education.

Relatively few addicted people seeking treatment have "disabled" networks with fewer than ten people and a single nonreciprocal group focused on their care. Those who are in this group may be mentally ill (e.g., Korsakoff dementia, alcoholic dementia, chronically psychotic). A thorough neuropsychiatric evaluation should take place early in treatment; neuropsychological, neurological, and medical assessment may also be needed. So-called skid row alcoholics living on the periphery of society may also fall into this category.

Assessment that incorporates members of the patient's ISN can serve several purposes: elaboration of a complete assessment, communication to the patient regarding the consequences of his/her behavior on those who care about him/her, and enlisting ISN members in intervention and recovery (Speck and Attneave 1973). Ongoing treatment that involves ISN members committed to the patient's

recovery aids in social network reconstruction while alerting network members to the need of reasonable expectations during the various stages of recovery (Galanter 1993).

Contingency contracting therapy weds social network intervention with a variety of psychological and pharmacological therapies (Bride et al. 2010). For example, a family member may administer an antagonist medication (e.g., disulfiram, naltrexone) to the patient in return for continued residence at home, or an employer may provide the same service in return for continued employment. Attendance at therapy or self-help sessions may be linked to various "rewards" in a similar fashion.

6.4.3 Artifactual ISNs in Recovery

Most people in a community have a normal social network and do not want additional network members. Since such relations require reciprocity, regular contact, and long-term emotional commitment, there is a self-limiting component to ISN size. It cannot grow beyond finite limits. Moreover, the network tends to accrete in groups rather than solely via individuals (although individual contacts can grow to subsequent group affiliations). Such affiliations also grow over time, almost like a courtship, in a series of small-but-reciprocal events, as trust and friendship develops. Thus, acquiring new individuals and groups poses a major challenge during recovery.

During the early period of recovery, a number of created or artifactual groups are available to the recovering person. These groups can include one or a few mutual-help groups (e.g., Alcoholics Anonymous) and perhaps a treatment team or case manager (Willenbring 1995). Certain community organizations open to all can provide a nidus for later affiliations (e.g., church committees, neighborhood political committees, hobbies or pastimes). Each culture and community contains its own entrees to such groups. Even in remote rural communities of a few hundred people, recovering people can rebuild a functional social network (Westermeyer 1982).

Recovering people can also be on the lookout for people whose social networks have been depleted and are expanding. People migrating to a new community typically rebuild their social network within several months. Those starting a new job, school, or training program may be open to new affiliations. A limiting factor for the recovering addict is the need for sober members in at least some of his or her social network and the absence of addicted people in the remainder of the network.

6.5 The Community and Addiction

Some communities are more addiction friendly, some are more recovery friendly, and many possess elements of both. Perhaps the most important pro-addiction environmental factor is a high prevalence of people using substances excessively

(Hughes et al. 1974). Widespread excessive use reduces social inhibitions against use. Having a large number of substance merchants also contributes to widespread use, as it increases access and – if market forces are at work – reduces the cost. Absence of restrictions against sale to youth or intoxicated persons, or unlimited hours of sale, fosters widespread use (Smart and Murray 1983).

Widespread intoxication in a neighborhood or illicit sales can, in time, undermine a neighborhood (Fagan 1989). Several avenues promote this outcome. Widespread intoxication leads to property crime (to purchase psychoactive substances) and interpersonal crime (due to increasing discord and disinhibition). Drug sellers become the role models for youth, due to their relative wealth and apparent power. Faced with these daily realities, working families involved in raising their families move elsewhere. Property values drop and licit retail stores move elsewhere. In many such settings, security falls as police abandon the neighborhood or cannot be deployed in adequate numbers due to the falling tax base. Corruption of elected officials and other governmental workers often emerges (Westermeyer 1982).

The current prevalence of addictive disorders can reach crude prevalence rates (i.e., total population rate) as high as 10–12 %. Examples include Southeast Asian and South Asian communities that raise opium poppy (Westermeyer 1981) and American native reservations with high alcohol and drug rates (Kinzie et al. 1992). Since most addiction in these communities occurs in those aged 18 years or older and adults comprise about half of the community, the adult prevalence rates are twice as high, in the range of 20–25 %. Since men in these settings have rates two or three times that of women, current adult male rates run around 26–38 % and adult female rates run around 10–26 %. Two additional factors argue for lifetime risks of addiction that exceed these crude prevalence rates: some of the younger adults will develop addiction during their adult years in the future, but have not done so yet (Bean and Zinberg 1981), and some of the addicted adults in the population have already died at an early age from substance-related causes, so that addicted people are underrepresented (Berne 1964). Although no firm lifetime rates are available for these high-rate communities, extrapolations from current prevalence rates, risk factors favoring future addiction in some adults, and early removal of addicts from the population through premature death suggest that even higher lifetime rates, perhaps 15–30 % in women and 30–50 % in men, can exist. Burdens in such communities include child neglect and abuse, malnutrition, marital disruption, violence, infectious disease, poverty, crime, and premature death (Westermeyer 1999). Although some community leaders in such settings focus public attention and action on addiction, many others deny its existence and accuse clinicians or epidemiologists of exaggerating or lying about the extent of addiction in the community (Foulks 1989).

Addiction services within a community must be integrated to be successful. For example, failure to engage newly released prisoners in treatment produced a high drug-related mortality rate during the first 2 weeks post release (Farrell and Marsden 2008). Mortality is also high during the first month following discharge from opioid maintenance treatment (Cornish et al. 2010). Availability of chronic pain services may comprise a safety net for patients transitioning from one phase of addiction treatment to another (Barry et al. 2012).

6.5.1 State Government and Addiction

Actions by governmental bodies can greatly influence the rate and course of addiction in a society. Governmental efforts can be most effective and efficient when rates are low and decreasing. Conversely, governmental efforts are most apt to go awry when rates are high and increasing. Under such circumstances, the government striving to reduce the addiction rates is at odds with the large number of the populace who value heavy, excessive, widespread use. The latter group includes not only the heavy consumers, but also many others who profit from heavy, widespread use. Profiteers include basic producers (e.g., farmers, biochemists), manufacturers (distilleries, pharmaceutical companies, illicit gangs), transporters, wholesalers, retailers, bankers, advertisers (if the substance is legal), private security forces (if the substance is illegal), and government workers, altogether comprising a virtual army of citizens and public workers dependent on or corrupted by the industry (Suwanwela and Poshyachinda 1986).

Despite the myriad of obstacles, many governments have reduced widespread addiction over the last three centuries (Lowinger 1977). There is evidence from Mexican glyphs that Aztec laws limited alcohol use even earlier (Anawalt and Berdan 1992). Successful means of limiting or eliminating certain addictions have included the following:

- Taxes on import and/or sale of certain psychoactive substances (e.g., beverage alcohol, tobacco)
- Licensure to import, produce, or sell certain psychoactive substances in specific amounts
- Restriction of certain substances to medically supervised prescription use (e.g., opioids, sedatives, stimulants, cocaine)
- Constraints on density of retail outlets for certain licit psychoactive substances, as well as hours and days of sale
- Punitive laws against behaviors that undermine governmental authority with regard to psychoactive substances (e.g., bootlegging, illicit production), risky behaviors during use (e.g., driving, boating, flying, hunting), and actions that may engender addiction (e.g., sale to minors or intoxicated persons)
- Providing treatment for addicted victims of alcohol-drug epidemics while punishing those who illegally produce or distribute these substances or commit illegal acts while influenced by these substances (the so-called carrot and stick approach)

Governmental actions can also foster addiction and/or the consequences of addiction in numerous, often unintended ways, as follows:

- Placing tax revenues on psychoactive substances into the general revenues of the state, so that governmental officials seek to increase substance use as a means of increasing revenues (rather than targeting these funds to reduce addiction and address its consequences)
- Providing governmental funds for housing or unemployment incomes to addicted persons with no supervision or expectation for recovery while overlooking opportunities for community reinforcement of sober behaviors (Azrin 1976)

- Overlooking the propensity of simple-but-fundamental social interventions (such as prohibition, so-called "medical" use of addictive substances outside of ordinary channels, free unsupervised shelters for addicted persons) to produce large-scale effects opposite to those intended or predicted (Schwartz et al. 2011)
- Permitting various organs of governance or public sectors to avoid or undermine governmental efforts to limit or reduce addiction (e.g., health, education, law enforcement, taxation/important agencies, military units)
- Issuing psychoactive substances to military units (e.g., opioids, alcohol, cannabis, amphetamines, benzodiazepines) supposedly to increase combat efficiency
- Ignoring widespread addiction on local, regional, or national levels as a means of cultivating popular support, promoting one's own reelection, or emasculating public criticism
- Accepting governmental corruption by elected and appointed officials, as well as among frontline government employees
- Neglecting to ensure availability of mental health services, so that people treat their symptoms with alcohol and illicit drugs (Castaneda et al. 1994)
  See Sect. 4 for more on this topic.

6.5.2 The Sociocultural Milieu and Addiction

In numerous traditional societies in which psychoactive substances are used with minimal problems, a functional social group determined the occasion for use and amount used (Bennett and Ames 1985). The group was often the extended family, but could be a religious group or other social organization. Feasting and other celebrations (e.g., dance, song, stories, speeches) accompanied substance use. Across the world, alcohol was perhaps most commonly used substance, but tobacco, hallucinogens, and other substances were also used. Occasions for such celebration include annual feasts (e.g., New Year, harvest, religious holy days), life-cycle milestones (e.g., birth or naming day, adolescence, marriage, death), and various individual achievements (e.g., graduation, membership in an elite group, "potlatch" or giving away accumulated wealth). Child, adolescents, or young adults received supervised initiation (or ensocialization) into substance use, guided by a relative. Substance use outside of these boundaries comprised a culturally forbidden or taboo behavior. Under these circumstances, addiction was rare or even nonexistent. However, this well-organized entrée into use of a given substance did not protect the individual for addiction on other substances that did not involve this type of regulated orientation. In addition, adolescents can be ensocialized into the healthy use of only a limited number of substances (usually two to four in most cultures).

A second type of pathogenic orientation into substance use is more apt to result in addiction. This mode generally occurs within a non-kin peer group. Those conducting the ritual are often slightly older than the initiates. Females may instruct females, and males may instruct males; but if cross-gender familiarization occurs, typically males teach females. The setting is secular, rather than familial or

ceremonial. The main event is the use of the substance, its subjective effects, and the peer group experience. If the substance is illicit, it may occur in a surreptitious fashion (which may add to the excitement of the event and the subjective effects of the substance). Depending on the culture or the individual group, the coaching mostly occurs from early adolescence to early adulthood. It may occur when the person has left home (for school, work, or military service) or during individualization from the family to adulthood. Initially the peer group sets the occasion and perhaps also the amount of use. However, with time, individuals decide their own frequency or amount of use. With age, marriage, parenting, and work responsibilities, many people fall into a pattern of nonuse (if the substance is illicit) or mild-to-moderate use (if the substance is legal and culturally acceptable). Others choose heavy or excessive use, paving the way to addiction as a lifestyle (Westermeyer 1999).

Both patterns of instruction can occur in a given family, community, or culture. For example, alcohol use may be carefully taught within the extended family, while tobacco smoking may be learned from peers. This scenario would favor addiction to tobacco but nonproblematic use of alcohol. Supervised substance training may prevail in traditional societies with specifically traditional substances, such as alcohol, tobacco and hallucinogens (in the Americas), caffeine (in teas and coffee), and khat. Society-wide education in the use of certain other substances takes place infrequently for other substances, such as coca leaf or cocaine, betel-areca, opium and its derivatives, or industry-produced substances (sedatives, amphetamines, anesthetics, anticholinergics).

The use of substances can impede enculturation into adulthood by alleviating the anxiety or insecurity that accompanies acquisition of maturity. Maturity-related tasks consist of social performance (e.g., speaking or performing before a group), comfort with sexuality (e.g., conversing with the opposite sex, expressing affection, courting), and various interpersonal skills and problem solving (e.g., conversation, coping with confrontation, settling differences). If an individual can engage in these activities only under the influence of psychoactive substances, two problems ensue: maturation is delayed, with detrimental effects on self-confidence and self-esteem (Bean and Zinberg 1981), and the substance is needed to perform the task, setting the stage for eventual addiction, as a higher dose and more frequent use is required to alleviate social fears or performance anxiety (Berne 1964).

Psychoactive substance use may accompany certain types of work. For centuries, coca leaf, betel-areca, tobacco, and alcohol use have attended long hours of heavy or repetitive work (e.g., factories, road building). For tasks requiring heightened awareness or bursts of energy (e.g., hunting, warfare, athletics), some societies have employed stimulant use (caffeine, cola nut, khat, kratom). Traditional healers, spiritual leaders, or members of spiritual or healing associations (such as Zar-like healing cults across Asia) may use substances to facilitate trance. Depending on the culture and current practice, these substances have encompassed opiates, hallucinogens, tobacco, and other drugs. Rather than use drugs of any kind, some groups have employed fasting, sleeplessness, social isolation, silence, or repetitive music or dance as a means of achieving trance, communication with spirits, or healing.

Many workers around the world relax at the end of the work day with a variety of substances, including alcohol, caffeine, khat, tobacco, opiates, and cannabis.

Epidemics of addiction have occurred around the world over the last five centuries, beginning with epidemic alcohol use in Europe, epidemics of opium smoking across Asia and parts of Europe, and tobacco almost everywhere. Factors supporting these early epidemics comprised the following:

- Appearance of new substance forms, which were not subject to traditional customs (e.g., gin and rum in European countries where beer, ale, or wine had been traditional)
- Appearance of new modes of administration not subject to traditional mores (e.g., smoking opium replaced medicinal oral ingestion of opium)
- New substances (e.g., tobacco, cocaine) over which no traditions or rituals had governed use
- Profiteers who endeavored to increase use and thereby increase their profits
- Diverse, conflicting, or ambivalent beliefs and attitudes toward use, so that any given society could not act in a coherent fashion vis-à-vis the substance
- Delay in the appearance of epidemic consequences, so that addiction spread widely before the extent of the problem could be appreciated

As addiction spreads to epidemic proportions, it tends to do so in a hidden fashion during its early stages (Westermeyer 1982). This unique phenomenon is due to the consequences of addiction epidemics showing up in numerous sectors, including health, family life, productivity, child raising, property crime, interpersonal crime, economic burdens, and various other manifestations. Moreover, the spread occurs over years or even decades and centuries, unlike infectious disease epidemics that can devastate a population within weeks, months, or a few years. The low incidence of any one addiction-related index allows profiteers and other supporters to pass the occasional problem off as being unrepresentative, or "the small price" necessary in providing this new benefit or recreation or life enhancement to the population at large.

6.6 Addiction from International Perspectives

6.6.1 International Participation

Beginning five centuries ago, the largest addiction epidemics involved international trade. Substances were produced legally in one region (e.g., gin and rum in the Caribbean, opium in India, tobacco and cocaine in the Americas) and transported, often illegally, to countries in another region. Relatively safe and inexpensive international transport facilitated the trade. Large investments in production, transport, and security were secured from banks and profiteers – and sometimes even governments (Westermeyer 1987).

The scenario described above has continued in recent decades. However, several international organizations have united many countries against addiction. Government-supported organizations include the United Nations and its Narcotic

Control Board, the World Health Organization, and numerous other groups concerned with pharmaceutical production, crime, and drug trafficking. Several professional groups have formed international associations to oppose addiction, including physicians, pharmacists, police, and various nonprofit nongovernmental groups (NGOs).

6.6.2 Technology and Addiction

Recent centuries have produced numerous technological advancements that have contributed to addiction epidemics. One general trend has been the isolation of powerful chemicals from raw plant compounds (e.g., morphine and heroin from opium, cocaine from coca leaf). Another trend has been the spread of methods of administration, such as smoking from the Americans to the other continents, hollow needles and syringes for parenteral administration, and recent topical methods. Entire new compounds have emerged from the pharmaceutical industry, i.e., barbiturates, benzodiazepines, volatile inhalants, amphetamines, certain hallucinogens, and new opioid drugs. Rogue pharmacists and biochemists have produced "designer drugs" to produce specified effects. These trends continue.

Rapid means of transportation and easier international travel have reduced the time needed to travel from one place to another. Rapid safe transportation has also reduced the difficulty of marketing substances from one area to another. With increased profits and more secure, stable addiction markets, profiteers from many economic sectors are drawn to subsidizing addiction, either openly or behind various facades.

6.6.3 Addiction as a Transmissible Condition

Many health conditions pose international threats (e.g., HIV, influenza), while others appear more related to local conditions (e.g., heart disease, diabetes, schizophrenia). Although local factors can impede or accelerate addiction, nonetheless addiction can resemble the transmissible disorders. An evolving addiction epidemic in one country threatens its immediate neighbors, and sometimes other countries at a greater distance. For these reasons, international collaboration in studying successes as well as failures in reducing addiction stands to benefit all.

6.7 Discussion

Social-environmental factors weigh heavily in the etiology of addiction. In spite of genetic and psychopathological risk factors that are omnipresent, some communities, states, and cultures have nil-to-minimal rates of addiction (i.e., current prevalence <1 % crude prevalence). In settings with even moderate rates of addiction (i.e., 1–5 % crude prevalence rates), addiction can be the main contributor to crime,

family dysfunction, violence, and incarceration. At high rates (6–12 % crude prevalence rates), addiction may be the main precipitate of hospitalization, suicide, accidents, mental-emotional-behavior disorders, infectious disease, degenerative disease, nutritional disease, and even all-cause mortality (Westermeyer 1982).

Although social-environmental factors can be a major factor in addiction, these factors can also furnish potent prevention, early intervention, effective treatment, and successful rehabilitation for addiction. Therapeutic approaches can occur on the level of the dyad (i.e., the addict and one other person), family, intimate social network, neighborhood or village, local or state government, and various sociocultural entities. All social sectors can lend their powers to these efforts. Charitable organizations and foundations, churches and their clergy, clinics and their staff, community leaders, courts of law, departments of public safety, elected officials, hospitals, licensure bureaus within government, mass media, public health departments, schools and their teachers, universities, and other institutions can be part of the addiction problem or part of the solution to addiction.

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Cultural Aspects and Responses to Addiction

7

Robin Room

Contents

Abstract

The use of psychoactive substances and our interpretations of the effects of the substances are affected by culture, defined broadly to include social worlds and subcultures as well as tribal, societal, and linguistic groupings. Prototypical patternings of use include medicinal use, customary regular use, and festival and other intermittent uses (where the psychoactivity is most attended to). A fourth pattern, addictive or dependent use, was a conceptualization arising after the Enlightenment. Cultural norms may both encourage and discourage use and heavy use and may make the use more or less problematic. Cultural factors also shape responses to substance use, including the social handling of problematic situations and persons. Thus, there are characteristic differences between cultures in the institutional and professional location of the handling of substance use problems. In the modern world, there is substantial diffusion of practices and understandings between cultures, and in multicultural societies,

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drinking or drug use patterns often serve as markers of cultural distinctions. Despite all the diffusion, there are persisting cultural differences in thinking about, patterns of, and responses to psychoactive substance use.

7.1 Introduction

This chapter is concerned with cultural factors in addiction. In discussing cultural aspects, we are referring to shared beliefs, norms, and patterns of behavior, both about the use of psychoactive substances and about how the use should be interpreted and responded to. "Cultural" is used to mean pertaining to a variety of kinds and levels of collectivity. This can range from a small tribal group, for instance, the traditional inhabitants of Easter Island in the Pacific, to a large multinational aggregation, as in a discussion of how English speakers understand addiction, in contrast, say, to French speakers.

Often in discussing cultural factors, we are dealing with multicultural situations, with a diversity of cultures or subcultures. In such situations, the particular norms and behaviors of a group may serve as markers differentiating between groups, where most people drink alcohol, for instance, abstaining from alcohol may become a mark of difference for Muslims or Mormons (Room 2005).

We also use "cultural" here to refer to "social worlds" (Shibutani 1955; Unruh 1980) within a society in which understandings, norms, and behaviors are shared but in which the cultural boundaries are less marked. For instance, one can speak of a social world of heavy drinkers who know what is the expected behavior at the bar in a tavern in a particular society (Cavan 1966). Are male drinkers expected to buy drinks for each other, or does each always pay just for himself? What signals are being sent between a man and a woman when he buys a drink for her, and she accepts?[1] Among young adults in Oslo, Norway, for instance, "when men buy drinks for women, this may be interpreted as a negotiation for further intimacy" (Træen and Hovland 1998). Answers to such questions will be obvious to those within the social world, but may not be to outsiders.

7.2 Cultural Expectations About and Definitions of Psychoactive Substances and Their Effects

By definition, psychoactive substances change our mental state. But how we interpret that change, and how we behave under the influence, is strongly influenced by "set and setting" (Zinberg 1986) – including our expectancies about the effects, which in turn are influenced by cultural factors as well as previous experience. Although the psychoactive effect of tobacco may not register in the consciousness

[1]See "Buying and accepting drinks" thread on http://forums.plentyoffish.com/datingPosts8464582.aspx (accessed 16 June, 2013).

of a habituated cigarette smoker, in other circumstances, the effect of tobacco use may be so strong that the user is rendered unconscious, as early Spanish observers reported in describing tobacco use among native South Americans (Robicsek 1978). How those under the influence of a given dose of alcohol behave differs widely between cultures, as MacAndrew and Edgerton (1969) argued in their landmark work on *Drunken Comportment*. Whether or not someone taking LSD experienced a "bad trip" in the USA in the 1960s and 1970s, Bunce (1979) argued, was strongly influenced not only by subcultural expectations but also by the extent of sociopolitical controversy at that particular historical moment concerning the drug.

Three social patternings of psychoactive drug use can be distinguished as prototypical: medicinal use, customary regular use, and intermittent use. In many traditional societies, some drugs or formulations have been confined to medicinal use, that is, use under the supervision of a healer to alleviate mental or physical illness or distress. For several centuries after the technique for distilling alcoholic spirits had diffused from the Arab world to Europe, for instance, spirits-based drinks were regarded primarily as medicines (Wasson 1984). This way of framing drug use has been routinized and made subject to official control in the modern state through a prescription system, with physicians writing the prescriptions and pharmacists filling them. Drugs included in the prescription system usually are forbidden for nonmedicinal use (Babor et al. 2010), although the modern international drug control system has been fighting a losing battle to enforce this rule.

When a drug becomes a regular accompaniment of everyday life, its psychoactivity often is muted and even unnoticed, as is often the case for a habitual cigarette smoker. Similarly, in southern European wine cultures, wine is often differentiated from intoxicating "alcohol"; wine drinkers are expected to maintain their original comportment after drinking. This may be called a pattern of *banalized use*: A potentially powerful psychoactive agent is domesticated into a mundane article of daily life that is available relatively freely in the consumer market.

Intermittent use – for instance, on sacred occasions, at festivals, or only on weekends – minimizes the buildup of tolerance to a drug. It is in the context of such patterns that the greatest attention is likely to be paid to a drug's psychoactive properties. The drug may be understood by both the user and others as having taken control of the user's behavior and thus to explain otherwise unexpected behavior, whether bad or good (Room 2001). As in Robert Louis Stevenson's fable of Jekyll and Hyde, normal self-control is expected to return when the effects of the drug wear off. In light of the power this framing attributes to the substance, access to it may be limited – in traditional societies by sumptuary rules keyed to social differentiations and in industrial societies by other forms of market restriction, including outright prohibition.

In modern societies, a fourth pattern of use is commonly recognized: addicted or dependent use that is marked by regular use, often of large doses. Where such use for the particular substance is not defined in the society as banalized, addiction tends to be defined as an individual failing rather than a social pattern.

Conceptualizing repeated heavy use in terms of addiction means that the categorization becomes an explanation – an explanation of why the pattern of use continues, despite problems resulting from the use for the individual and often for others. The concept thus focuses not on the pattern of use in itself, but rather on an apparent inability to control or refrain from use despite adverse consequences.

The addiction concept became established for alcohol in general understandings of European societies in the period after the Enlightenment. Particularly as temperance movements sprang up in response to the waves of very heavy alcohol consumption that accompanied the Industrial Revolution, the addiction idea came into common use as an explanation of why backsliding was common among temperance members who had pledged to give up drinking (Levine 1978; Room 2003). In the late nineteenth century, the concept was extended by doctors to cover other psychoactive substances, and more recently popular and professional discourse has commonly applied it also to other behaviors (Marks 1990; Saïet 2011), though not without dispute (Jaffe 1990). Though the concept has diffused into many cultures, there are substantial differences in cultural understandings of what it characterizes and implies (Room 2006).

7.3 Norms Concerning Use and Related Behavior

The use of psychoactive substances in any society or cultural group is structured by norms concerning use and behavior while and after using. Laws and regulations on these matters, such as laws forbidding sales to or use by those under a certain age, or prohibiting driving after use, or regulations such as a church denomination's rubric specifying how leftover consecrated wine from a communion service it is to be handled ("reverently" consumed; Anonymous 1662), may be described as formal norms. At least as important in structuring use are informal norms concerning use, which are often highly differentiated according to the social context (Greenfield and Room 1997) and to the user's demographic and social position. Bruun's division between controls at the phases of use, of pattern, and of consequences (Bruun 1971b) – whether use at all is disallowed, or there are controls on the pattern of use, or controls aiming to insulate the use from adverse consequences – describes the main strategies of both formal and informal norms in limiting the damage from substance use.

It is important to note that norms may encourage use – and indeed heavy use – as well as discourage it and may make the use riskier or more problematic. Taking alcohol as an example, heavy drinking or drug use is not always a matter of individual choice, but in particular social contexts may be a strong expectation. For example, in cultures where buying rounds is customary, once the round has been established, a man drinking with a group of friends will face a strong expectation to stay and drink as many drinks as there are men in the group. In a Mongolian cultural group in China, competitive drinking is a norm: "a refusal to drink signifies a refusal to engage the other on equal and respectful terms. Drinking partners take turns challenging each other to drain the cup, and the cups

are inverted immediately afterward to prove the liquor is gone" (Williams 1998). Among young adult Italians, as also elsewhere in Europe, drinking games, enforced as a group ritual, serve the function of "becoming drunk quickly so as to amplify the effects of drinking: less shyness and disinhibition" (Beccaria and Guidoni 2002). Cultural expectations may thus facilitate heavy drinking and even enforce it, so that in some circumstances addiction or dependence might better be described as located at collective levels rather than in the individual's mind or body (Room 1973). This idea is carried by the French term *alcoolisation*, used concerning a society such as France when alcohol consumption was at its highest there in the 1950s (Jellinek 1954).

7.4 Cultural Factors in Responses to Substance Use

Intoxication and habitual use of psychoactive substances can be problematic in many ways for those around the user, and societies and cultures respond in many ways in efforts to limit or prevent the problems. Informal responses by those around the drinker, smoker, or drug user are very common (e.g., Hemström 2002; Hradilova Selin et al. 2009) – at levels ranging from a spouse's raised eyebrow to strenuous retribution.

Societies also respond to alcohol and drug problems at more formal levels. In the modern world, there is considerable uniformity across societies in the general roster of agencies and professions with responsibility for the social handling of problematic situations and persons. In most societies, there are hospitals and other health services and medical professionals, courts and police and judges, welfare institutions and social workers, and churches and other faith institutions and clergy. But none of these sets of agencies and professions have clear and unchanging custody of alcohol and drug problems. Typically, all of them handle some part of drug and alcohol problems, but drug and alcohol problems are not central to the jurisdiction of any one of them. The result is a diversity of competing models of how alcohol and drug problems should be handled (Bruun 1971a). As an eminent addiction doctor, Norman Kerr, put it already in the late nineteenth century: "in drunkenness of all degrees of every variety, the Church sees only the sin; the World the vice; the State the crime. On the other hand the medical profession uncovers a state of disease" (Kerr 1888).

There are characteristic cultural differences in the location of the handling of alcohol and drug problems. For alcohol problems, for instance, the welfare system has been the traditional central location in several Nordic countries; liver clinics within the medical system have played a major role in France and Italy; psychiatry has had a principal role in Switzerland and Austria (Baumohl and Room 1987; Klingemann and Hunt 1998; Klingemann et al. 1992). But it is also true that, in a given society, the handling of alcohol and drug problems has often changed over time – particularly because these are "wicked problems" (Rittel and Webber 1973) where whatever solution is in effect will seem inadequate. As Bruun (1971a) remarked about the Finnish history of the social handling of alcohol problems,

"the consistent frustrations concerning the relative lack of success in fighting alcoholism made [Finland] move compulsively from one model [of response] to another."

The responses to alcohol and drug problems, both informal and formal, are thus just as subject to cultural definitions and norms as are the substance use and related behaviors. The responses are influenced both by the cultural definitions and norms concerning the substance use and by cultural beliefs and practices concerning appropriate responses. For the formal responses, general cultural and societal understandings and practices concerning the social handling of social and health problems also come into play.

7.5 Intercultural Influences and Diffusion

No man is an island, and no cultural group in the modern world is completely on its own. A particular solution to a set of problems worked out in the cultural conditions of one society may travel far. Thus there is much about the ideas and organization of Alcoholics Anonymous that reflects cultural understandings and practices in a particular society, the United States (Mäkelä et al. 1996; Room 1993). But AA has diffused widely across the world, into cultures with considerable differences from US society. Even so, it is clear that the patterns of diffusion of AA show some regularities in terms of which societies it has flourished in, and these regularities tell us something both about core characteristics of AA and about patterns of culture (Mäkelä 1991). And to some extent, AA practices have been adapted to the local culture (Eisenbach-Stangl and Rosenqvist 1998). Furthermore, even where AA was seen as culturally alien in some way, the news of its existence stimulated adaptations seen as more culturally congenial – and often the outcome has been AA and the adaptation coexisting side by side (Room 1998).

We have already mentioned above the tendency of cultural groups in multicultural societies to define themselves in distinction from each other, with drinking or drug use practices fairly often used as markers of the distinctions. On the other hand, it is clear that there is also some assimilation: Immigrant groups take on practices from the receiving society, often forming a new cultural bricolage (Room 2005). Influences and diffusion are also common between societies and cultures. Such influences are carried by four major forces: mass media, producers and other economic actors, intergovernmental bodies and agreements, and the professions. News reports, television and film entertainment, and now also Internet channels convey information and images between cultural groups, perhaps particularly between youth cultures in different societies. In an increasingly globalized world with diminishing trade barriers, global corporations and other economic actors (and their equivalents for illicit drug markets) actively and tirelessly try out promotion methods and materials which have worked elsewhere in new cultural settings. Dissemination and influence also flow through the international drug and tobacco treaties and the agencies which implement them, as well as increasingly through other agencies such as international nongovernmental organizations in a

cross-national policy community. And doctors, police, and other professionals, through professional societies, journals, newsletters, and meetings, diffuse ideas, evidence, and practices internationally.

Despite all the dissemination, cultural differences persist. In terms of cultural differentiations in psychoactive substance use and problems, and in the societal and cultural responses, it is possible to point to trends both of change and of stasis, both of convergence and of divergence, depending on where one looks. In thinking and acting across cultures concerning alcohol and other drugs, it is wise to take into account that even matters that are taken for granted in a given society or culture, or that are assumed to be universally valid in a profession's thinking, are often understood differently in different cultural traditions.

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Prevention Strategies and Basics

8

Gregor Burkhart and Roland Simon

Contents

Abstract

Prevention has the potential to be effective in changing substance use and related behaviors such as delinquency, violence, and sexual behavior. Interventions that achieve this do not solely inform people about the dangers of drugs but also focus on the key determinants of successful socialization, now confirmed by neuropsychological research: social norms and control, executive and social skills, as well as impulse control. Thus, universal prevention addresses the population at large and targets the development of skills and values, norm perception, and interaction with peers and social life; selective prevention addresses the vulnerable groups where substance use is often concentrated and focuses on improving their opportunities in difficult living and social conditions;

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and indicated prevention addresses vulnerable individuals and helps them to deal and cope with the individual personality traits that make them more vulnerable to escalating drug use. While these prevention types predominantly use persuasion, prevention can complementarily and effectively change human behavior by modifying its social, physical, and economic context. Environmental prevention uses these means to subtly alter social cues and norms and their perception. Effective examples range from intervening at society level through market regulations of alcohol and tobacco, changing the physical environment of party settings, to more rule setting and monitoring within families. The challenge for drug prevention lies therefore in helping people to adjust their behavior, capacities, and well-being in fields of multiple influences – such as social norms, interaction with peers, living conditions, and their own personality traits – in order to reduce risk behaviors related to substances.

8.1 Introduction

Drug prevention is traditionally conceived of as interventions or policies to avoid or delay the initiation into substance use by adolescents. It is a key element of national and international drug policies. Prevention is thought to act on the demand reduction side of drug interventions, helping people to avoid the use (or problem use) of psychoactive substances and their negative consequences. This understanding of prevention is complementary to treatment (which targets recovery and cure) and harm reduction (which helps people avoid the secondary negative effects of the use, or problem use, of addictive substances).

8.1.1 Neuroscience and Prevention

The most obvious contribution of neuroscience to prevention is that it has explained why and how the developing brains of adolescents are particularly vulnerable to the noxious effects of alcohol, tobacco, and illicit drugs – the greatest neuronal reshaping processes of the human life cycle take place during adolescence. Psychoactive substances used in this period therefore have longer lasting and more deleterious consequences in the neurobiological substrates of human development. Prevention work can use findings from neuroscience to tailor interventions to the peculiarities in the neuropsychological functioning of adolescents. However, research (outlined below) has found that the usual approach of information provision and simple warning strategies has little effect on how adolescents take decisions and deal with risk. Professionals and policymakers have only just started to use these new insights.

8.1.1.1 Personality Traits and the Common Liability Model

Another, less publicized, contribution of neuroscience to prevention has been to (re) introduce concepts such as personality traits and temperament as risk factors, giving a longer-term perspective to prevention, which starts in early childhood. Many

prevention professionals still see substance use as the main risk factor for substance use disorders and addiction and therefore conclude either that substance use must be prevented altogether or that it must be detected early and discouraged. While early use is a necessary step, other variables may be of crucial importance in the transition from use to substance use disorder. In fact, the same variables that predict initial acute drug effects and early use may significantly contribute to continued use, escalation, and dependence (De Wit and Phillips 2012). Traditional prevention work focuses exclusively on substance use and is based on a stage model where the use of legal substances precedes and anticipates the use of illicit drugs. More recent research has introduced an alternative view, the common liability model, which suggests that early-manifesting personality traits such as neurobehavioral (i.e., cognitive, affective, and behavioral) disinhibition predict both early initiation of substance use and rapid escalation into problem use. Other problem behaviors can also have this effect, especially if both parents have a substance use disorder (SUD). Longitudinal, prospective studies with Finnish twins found that the liability to initiate tobacco smoking predicts illicit drug use and suggested that shared genetic and environmental influences may be related to the use of tobacco and illicit drugs (Huizink et al. 2010). Early externalizing behavior also suggests significant and shared underlying genetic and environmental influences that may lead to later substance use (Korhonen et al. 2012).

Other personality traits, such as high levels of pleasure seeking and low levels of shyness and avoidance, have shown in prospective studies to increase the risk of progressing from smoking to several measures of cannabis use (Creemers et al. 2009). A longitudinal study (Malmberg et al. 2012) showed that hopelessness and sensation seeking were predictive for using alcohol and tobacco. The latter was also correlated with marijuana use.

In a recent paper, Sloboda et al. (2012) provide an exhaustive revision of the risk factor models relevant for prevention, which include many developmental factors in early childhood that interact with environmental factors in family and school in later childhood and adolescence.

Instead of targeting drug users generally, these findings point to a need for more sophisticated prevention interventions that specifically target individual vulnerability traits that are not a priori substance use related. This is the premise for indicated prevention.

8.1.1.2 Neuroscience and Social Norms

Recent findings in the field of neuropsychology (Steinberg 2008) have shed light on why information provision does not deter young people from drug use and other problem behaviors. Findings show that their behavior is determined more by social context than by individual choice.

Judgement of risk seems to be a crucial element at this age. Galvan et al. (2006) found that the activity of the nucleus accumbens within the limbic system, responsible for drive and impulsivity, begins to increase in adolescence, while the prefrontal cortex, responsible for behavioral control, is not yet fully developed at this age. This imbalance alone does not necessarily result in impaired judgement

of risk. However, an additional developmental process, the increase of oxytocin receptors in the limbic system during adolescence, explains why adolescents – compared with children and adults – respond more intensely to emotional and social stimuli and have increased awareness of others' opinions (Steinberg 2008). There is an important overlap between neural circuits responsible for social information processing and those for reward, so that reward seeking is increased in the presence of peers when the brain's socio-emotional system is stimulated.

The interplay of these processes suggests why adolescents more often take risks (especially substance use and reckless driving) in peer group environments. When adolescents are alone or not emotionally excited, the cognitive control of the prefrontal cortex is strong enough to control or regulate impulsive and risky behavior. Under these conditions, adolescents perform risk assessment of situations and behaviors similar to adults. The more developed limbic regions only manage to override the less developed behavioral control of the prefrontal cortex when young people are with peers or emotionally aroused, resulting in poor and impulsive decisions. High sensation seekers in particular seem to learn to delay gratification by engaging in risky behavior such as substance use, which might provide them with experiences that lead to greater patience in anticipation of long-term rewards (Romer et al. 2010).

Therefore, it seems to be normative, biologically driven, and to a certain degree inevitable and functional that adolescents are prone to risk-taking during adolescence. Mature judgement needs time to develop, and therefore cognitive–informative techniques seem unlikely to make adolescents wiser, less impulsive, or less shortsighted.

The considerations above have manifold implications for prevention.

(a) They help to explain why information provision has little impact on behavior, especially in this age group.
(b) They offer explanations for the harmful effects of mass media campaigns that increase normative beliefs, giving the implicit impression that most or many people do engage in a given problem behavior.
(c) They help to explain why drug legislation, which prosecutes individuals, often fails to dissuade adolescents from continuing to use drugs (Scarscelli et al. 2012). School sanctions, on the other hand, may have important long-run benefits (Waddell 2010) as they have high social visibility. Informal social control and social sanctions (from family and peers) may have more of an impact than the certainty and severity of formal sanctions (Paternoster 1987).
(d) They provide the theoretical underpinning on why adolescents – who are unaffected by possible legal sanctions – are heavily influenced by social norms, peer environments, and social control. In fact, "in places where informal social controls have been weakened, young people tend to see delinquent behaviour as a sign of strength, incarceration as a rite of passage, and law enforcement as illegitimate" (Berman 2012). Reinforcing informal social controls and changing the perception of normality are core objectives of environmental prevention.

8.1.2 Logic Frame

Section 8.1.1 described a number of factors influencing the risk of developing problematic patterns of substance use. The following section aims to show that the challenge of prevention is more than just avoiding or delaying substance use. Instead, it should help young people adjust their behavior, capacities, and well-being in fields such as living conditions, social norms, interaction with peers, social status and opportunities, and their own personality traits, drawing from the findings of evidence-based interventions in all these fields. Prevention could therefore be defined as evidence-based socialization where the primary focus is individual decision making about socially appropriate behaviors. Its aim is not solely to prevent substance use or to delay initiation but also to reduce intensification of use or prevent escalation into problem use. Socialization, in this context, means to transfer culturally acceptable attitudes, norms, beliefs, and behaviors to young people and to respond to cues for risky behaviors in an appropriate way by helping them to develop adequate impulse control.

Socialization takes place under the influence of family, schools, and society. The concept of environmental prevention has therefore been added to the three classical prevention strategies defined by the Institute of Medicine (Mrazek and Haggerty 1994) based on addressees' overall level of vulnerability, which was found more practical for the substance use prevention field than the medical paradigm of primary, secondary, and tertiary prevention. While the latter works fine for the natural course of, for example, cancer and infectious diseases, it seems less adequate to describe human behavior.

Mass media campaigns are the most instinctive form of prevention, and we will review them at the very start of our overview. These campaigns assume that informing and warning people about the dangers and consequences of a specific behavior is enough to prevent them behaving in a particular way. This is a problematic assumption, as we have seen above. Adolescent behavior seems to be little influenced by purely cognitive processes, and a number of different factors and processes intervene between the perception of factual information and adolescents' behavior.

The four main prevention strategies described below address the most relevant spheres of behavior influence: social norms and occasionally inequality are targeted by environmental strategies, interaction with peers and social life by universal prevention, social conditions and exclusion by selective prevention, and personality traits by indicated prevention. This simplified classification provides us with an overview of the different preventive approaches taken. Prevention can also be segmented by the level of environment on which it is acting. Bronfenbrenner's (1979) ecological systems theory conceptualizes as follows: macro level interventions, referring to those at societal and state level (e.g., legislation and taxation); meso level, which are at the level of communities, schools, and other setting; and microlevel, defined as proximal environments such as the family or peer groups.

Each part in Sect. 2 refers to the available evidence and describes trends and examples. As the majority of prevention activities focus in practice on substance use and problem behavior in general, they do not differentiate between alcohol, tobacco, and illicit drugs.

8.1.3 Assessing the Effectiveness of Prevention

While there has been a long-standing tradition in the field of prevention of welcoming any type of preventive measures – taking the good will for good results – evidence is now playing a crucial role in prevention work. However, the very nature of the intervention and target behavior makes research even more challenging than in the fields of treatment or harm reduction. Most prevention strategies address their target group at a very young age. This implies that there will be a long period of time between intervention and assessment of the outcome, which is a challenge to methodology (many influences will have to be taken into account), sample size (which inevitably shrinks over time), and research funding and organization. In all fields of research such long-term follow-ups are extremely rare. Prevention also tends to be generic, while outcome behaviors with respect to drug use and drug-related problems are specific. This again makes it more difficult for research to prove a logical link between intervention and envisaged outcomes. The conclusion drawn from this long list of difficulties and problems is not to discredit prevention interventions because they are difficult to evaluate but instead that existing findings should be critically evaluated to try to further improve the available evidence.

8.2 Prevention Strategies: Definitions and Effects

8.2.1 Mass Media Campaigns

A large proportion of the general public and substantial numbers of policymakers have, for some time, seen drug prevention as purely informing or warning young people about the effects or dangers of drugs. Quite logically then, mass media campaigns were often the first choice of prevention intervention.

Mass media campaigns can reach large and heterogeneous audiences and have shown to be beneficial in promoting some health behaviors like healthier nutrition, physical activity, and participation in screening for breast and cervical cancer (Wakefield et al. 2010). However, they seem to be much less successful in discouraging problem behaviors. While some positive effects on tobacco smoking have been found, there is actually no evidence that simply informing adolescents about the effect of drugs has a beneficial impact on their illicit drug use, as a recent Cochrane Review (Ferri et al. 2013) confirms. Since mass media campaigns seem to be more effective in tackling adolescent use of legal drugs, and when they target parents instead of young people (Crano 2010), perceptions of normality seem to play an essential role in their success and failure.

A worrisome case study for this is the evaluation of the National Youth Anti-Drug Media Campaign (1998–2004) in the USA (Hornik et al. 2008). It found – besides zero effects overall – that greater exposure to the campaign was associated with increasing intention to use cannabis (and even actual use) in some subgroups that previously had little interest in the drug. The analysis found evidence that these effects were due to an increase in the perceived popularity and prevalence of marijuana use through the campaign. Also, in the evaluation of Scotland's Know the Score cocaine campaign, Binnie et al. (2006) found that 11 % of those exposed to it claimed that they were more likely to use cocaine after the campaign compared to before. There is another reason for being cautious with warning campaigns that, for example, describe the negative outcomes of first using marijuana. If non-using adolescents realize that the harms of marijuana use are not as grave as they had been led to expect, their intention to use it might intensify considerably (Skenderian et al. 2008).

It is an important ethical concern that mass media campaigns may have iatrogenic effects – by increasing normative beliefs, resulting in higher intentions to use. This is even more problematic in this case, as the target population has typically not requested this (potentially harmful) kind of social intervention, and the organization funding and/or running the campaign has taken the initiative.

Against this background, the lack of adequate evaluations of media campaigns is even less acceptable – in Europe, only the Netherlands and Scotland/the UK have assessed effects of these campaigns on behavior or intentions, while the large majority of reported campaigns have not been evaluated at all. A few evaluations in Europe (Bulgaria, Denmark, France, Netherlands, Sweden, and the UK) have merely assessed how people perceive the campaign and its impact on their knowledge but were not able to assess if people changed their attitude or behaviors in the intended direction.

8.2.2 Environmental Prevention

Environmental prevention strategies aim to alter the immediate cultural, social, physical, and economic environments in which people make their choices about drug use. These strategies typically focus on social norms and climate (e.g., in schools) instead of persuasion and tend to address behavioral problems, for example, violence. This approach takes into account that individuals who might become substance users are influenced by a complex set of factors in their environment, including social norms, defining what is considered normal, expected, or accepted in their reference group; the rules or regulations and taxes of their state; the publicity messages to which they are exposed; and the availability of alcohol, tobacco, and illicit drugs. Environmental prevention strategies often entail changes at the macro level (legislation or society), such as market control using taxes and publicity bans or coercive measures including age controls and tobacco bans, which are effective but often resisted in some sectors of the population. These strategies alter the system of environmental – often unconscious – cues that influence

behavior, such as images and associations or the observed behavior of others. Since certain industries try to use these cues in their own interest, the term "industrial epidemics" has been coined for obesity, tobacco, and alcohol use (Jahiel and Babor 2007). Public regulation and market intervention are seen as the only evidence-based mechanisms to prevent the harm caused by commodity industries (Moodie et al. 2013). But efforts to create protective and positive school and family climates also belong to environmental prevention. Their modus operandi is not persuasion but positive "scaffolding" in the sense of providing opportunities, stimuli, and encouragement for change in confined contexts.

8.2.2.1 Environmental Influences in Schools

There is evidence that the school climate (e.g., the "alienation" of pupils from school) and the nature of the school environment substantially influence substance use and violence in school. Students' perceptions of whether they are treated fairly, school safety, and teacher support are also related to substance use. Interventions that increase student participation, improve relationships, and promote a positive school ethos (involvement, engagement, and positive teacher–pupil relations) therefore appear to reduce substance use. Programs based on this concept have shown to be transferable between countries (Markham et al. 2012).

Other strategies at the meso level include municipal strategies to reduce public nuisance, drug "policies" in schools, targeted policing, conditional venue and event licensing, fines and venue design guidelines, and community action strategies such as neighborhood watch schemes.

8.2.2.2 Environmental Influences on Nightlife

The known environmental determinants of alcohol abuse and violence also apply to nightlife settings: dirty conditions, poor ventilation, high levels of noise and music, low comfort, high density of patrons, predominant patronage by males, high numbers of intoxicated patrons, and high boredom (Miller et al. 2009). A European review (Hughes et al. 2011) found that important environmental contributions to alcohol-related problems include a permissive environment, discounted drinks promotions, poor cleanliness, crowding, loud music, and poor staff practice. Changing the environment also offers club owners and managers an approach that is less disruptive, which may motivate them to try it. Environmental approaches to reducing drug use and other risky behaviors may be more profitable for a business, improve its image, reduce the risk of city and police interference, and limit problems in its neighborhood (Miller et al. 2009).

Two European reviews of prevention interventions in nightlife settings (Bolier et al. 2011; Calafat et al. 2009) conclude that they can effectively reduce high-risk alcohol consumption, alcohol-related injury, violent crimes, access to alcohol by underage youth, and provision of alcohol to intoxicated people. However, some popular types of intervention (such as providing information or pill testing) were not considered evidence based. Interventions such as "responsible beverage services" or "designated driver programs," often backed by the industry, are less effective, especially if they are not enforced. The most effective strategies were

those that combined training, cooperation, and enforcement with "classical" environmental measures such as taxation, reduced blood alcohol concentration (BAC) limits for driving, and reinforced minimum legal purchasing age.

8.2.2.3 Environmental Influences Within Families

Substance use is influenced by social modelling by a person or group that is perceived as an authority or inspiration. Later in this chapter we will describe family-based programs that aim to improve the behavior of children and young people through better parenting. In this section we address some aspects of families that are not necessarily related to direct parent–child interaction but instead form part of environmental action on youth that might also include how young people select their social environment.

One aspect is the amount of pocket money, which has been found to be associated with increased prevalence of risky alcohol use (Bellis et al. 2007) and higher odds of smoking, getting drunk, using cannabis, and using ecstasy, even after controlling for socioeconomic status, gender, delinquency, parental supervision, and having a risk-taking personality (McCrystal et al. 2007). The findings are inconclusive on the influence of families' socioeconomic situation. In one French study (Legleye et al. 2012), adolescents from affluent families were more prone to experimentation with cannabis and to use it at low levels but had lower levels of frequent, heavy, or problematic use than those from other socioeconomic status categories. In a study in the USA, however, higher parental income was associated with higher rates of binge drinking and marijuana use (Humensky 2010).

How parents tell their own substance use history may also play a role. A recent study found an association between parents admitting their own past drug use in detail and teenagers having a more positive attitude to substances (Kam and Middleton 2013).

Parental ingenuousness about their offspring's substance use can have a protective function in the sense of a Pygmalion effect. In a longitudinal study (Lamb, C., & Crano, W.D. under revision#), adolescent users whose parents indicated that their children used marijuana at baseline were more than twice as likely to continue compared to children of parents who assumed that their children had not initiated marijuana use, even if this assumption might have been wrong. The assumed effect of this "ingenuous" prophecy resulted in a 39 % decline among the original sample of users while the "realist" prophecy resulted in a 4.3 % increase in use among nonusers at baseline. When parents had (maybe wrongly) assumed their children's marijuana use at baseline, these young people were 3.3 times more likely to begin using it compared to the other group. These findings indicate that parental trust – even if not based on facts – might have a positive effect on drug use behavior. A better assessment of the "real" situation, such as through testing, might destroy this Pygmalion effect and cause the situation to deteriorate. Obviously, monitoring and family rules play major roles in creating protective environments, but since such elements imply an active role by parents, we discuss those in the section dedicated to family-based prevention.

8.2.2.4 Environment, Social Norms, and Substance Use

Even if environmental prevention targets predominantly legal drugs and antisocial behavior, its approaches are important for the whole prevention field because early, widespread, and accepted use of alcohol and tobacco is associated with illicit drug use in many countries. Alcohol has a key role in the initiation of illicit drug use, especially among adolescents: European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) analyses of general population surveys in nine European countries (see Further Reading) showed an increased prevalence of amphetamine and ecstasy use among frequent or heavy users of alcohol. European School Survey Project on Alcohol and Other Drugs (ESPAD) data for 22 countries showed that 86 % of the 15- to 16-year-old students who had used ecstasy during the last month had also consumed five or more alcoholic drinks on one occasion. Similar relationships were found for alcohol with cannabis and cocaine.

In prospective longitudinal studies, tobacco smoking has been shown to mediate the initiation into cannabis use (Mayet et al. 2010; Vega and Gil 2005) and predicts an earlier initiation (Agrawal et al. 2013). It seems that the social and physical contexts of consumption are influencing the level of alcohol, tobacco, and illicit drug use in the same way. Environmental prevention focuses on these contexts.

The effectiveness of environmental prevention is well established in the alcohol and tobacco fields. At the macro level, taxation and regulations have been found to be effective, reducing alcohol use and related problems (Wagenaar et al. 2010). Increases in the minimum price of alcoholic beverages in Saskatchewan, Canada, have substantially reduced alcohol consumption (Stockwell et al. 2012). At the meso level, a study in Glasgow, Scotland (Young et al. 2013), on outlet density and proximity found that 15-year-old adolescents living within 200 m of an alcohol-selling outlet were more likely to drink frequently than were adolescents living in areas with less accessible alcohol-selling outlets. This suggests that certain alcohol behaviors (e.g., binge drinking) may be linked to the characteristics of alcohol supply in the area. Similarly, a study with the same age group in Switzerland (Kuntsche and Kuendig 2005) suggests that alcohol outlet density and related perception of adolescent drinking in public are positively correlated with individual alcohol use among adolescents. In the USA, a study (Plunk et al. 2013) of more than 39,000 subjects found that a legal age of below 21 years for buying alcohol was associated with an increased risk of binge drinking later in life. Additionally, drinkers who lived in states with lower minimum drinking ages were more likely to drink heavily, while they were not more likely to consume more alcohol overall, or to drink more frequently. Binge drinking was most pronounced among men who did not attend college. Among college students, however, previous studies' findings were inconclusive about the effect of the minimum drinking age (Wagenaar and Toomey 2002).

While alcohol and tobacco policies and their effectiveness are discussed in other chapters in this book (▶ Chap. 9, "Regional and Cultural Aspects of Prevention"), the following section focuses on the common effects and trends across substances and behaviors. Starting with the observation that prevalence rates for cannabis smoking were found to fall among European adolescents after more restrictive

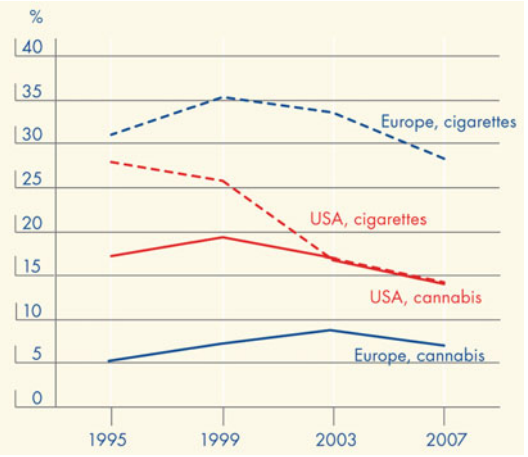

Fig. 8.1 Trends in last month prevalence of cannabis use and cigarette smoking among 15- to 16-year-old school students in 17 European countries and the USA

policies on tobacco smoking were introduced, one might assume some link between trends in the use of licit and illicit substances (Fig. 8.1).

Besides the perceived availability of substances, normative environmental aspects such as cultural values, descriptive norms, and the social acceptance of use seem to influence initiation into problem behavior and substance use (for more details on this, see ▶ Chap. 9, "Regional and Cultural Aspects of Prevention" in this book). Kuntsche and Jordan (2006) confirmed that close contact with substance-using peers is strongly related to individual substance use. Students who saw others attending school while intoxicated with cannabis, or taking cannabis on the school premises, used more cannabis themselves and had more cannabis-using peers. Similar relations were not found for alcohol. The authors suggest establishing an overarching environment of disapproval as an effective means of preventing cannabis use by adolescents.

Normative beliefs are important factors in the success or failure of interventions, and prevention work needs to address them (McAlaney et al. 2011). While several studies confirm that behavioral change is mediated by descriptive norms, the social norms approach has to be used with caution as social groups may also develop minority norms that deliberately deviate from the healthy descriptive norm that is being promoted. According to optimal distinctiveness theory, people adhere to social norms of highly valued groups that can simultaneously satisfy their needs to belong and to be different. For instance, messages that portray nonusers as a large and undifferentiated majority may not be as successful as messages that emphasize the uniqueness of nonusers (Comello 2011).

8.2.2.5 The Prevention Paradox

It is unlikely that environmental prevention will have much of an impact on the behavior of highly vulnerable individuals. However, the prevention paradox postulates that the majority of alcohol-related problems in a population are associated with low to moderate drinkers simply because they are much more numerous than heavy drinkers. A study in 23 European countries (Danielsson et al. 2012)

confirmed this prevention paradox for adolescent boys and girls for measures of annual consumption and heavy episodic drinking; similar results were found in Brazil. There is also some evidence for the validity of this phenomenon for other substances. Stockwell et al. (2004) confirmed it for regular tobacco, alcohol, and cannabis use among 15- to 16-year-olds. Still, there are limitations to this concept. A minority of people with frequent heavy episodic drinking accounted for a large proportion of all problems in one study (Danielsson et al. 2012), and Stockwell et al. (2004) found that most illicit drug use occurred in the high-risk group, 15 % of the sample.

The practical consequence of the prevention paradox is that all available approaches should be used: environmental and universal prevention strategies should aim to reduce initiation and overall levels of substance use, and targeted strategies should address particularly vulnerable subgroups and individuals, addressing harm related to early-age drug use or frequent cannabis use.

In summary, there is evidence for the beneficial effects of environmental prevention at the macro level (the state), at the meso level (recreational settings and schools), and above all at the microlevel (in families); and there are beneficial effects beyond substance use alone. More elements of environmental prevention should therefore be used to complement and support persuasive prevention strategies. It should be noted, however, that vulnerable subgroups and individuals also need targeted interventions, which will be described in the following sections.

The concepts of universal, selective, and indicated prevention are used to classify different preventive approaches in the following sections, based on differences in the vulnerability (and risk) of the target group. For universal prevention, all members of the population are assumed to share the same general risk for substance use problems, although the risk may vary greatly between individuals. Selective prevention applies social and demographic indicators that roughly indicate increased levels of vulnerability among some groups such as marginalized ethnic minorities, youth in deprived neighborhoods, young (drug law) offenders, vulnerable families, or some settings (such as clubbing environments). While these, often readily available, institutional or demographic indicators can help to identify groups where problem drug use is more likely to be concentrated, they cannot tell us anything about the vulnerability of any individual in such a group. In indicated prevention, however, vulnerable individuals are screened and needs have to be defined on the basis of "properly diagnosed" risk conditions, such as attention deficit disorder or conduct disorder.

8.2.3 Universal Prevention: Intervening with Populations

Universal prevention addresses the population at large, regardless of differing vulnerabilities of individuals or subgroups. It aims to reduce substance-related risk behavior by providing necessary competences to avoid or delay initiation into substance use, acting like a "behavioral vaccine." In Europe at least, universal

prevention predominantly takes place in schools, as they facilitate access to the largest target populations.

The overall effectiveness of school-based (universal) prevention has been repeatedly questioned, but there is abundant evidence from reviews (Bühler and Kröger 2008; Faggiano et al. 2008; Foxcroft and Tsertsvadze 2011a; Midford 2010) that programs based on the social influence approach have consistently been more effective than programs based on any other approach. The approach consists of components such as social skills training (listening, making compliments, empathy, and communication), strengthening personal skills (goal setting, coping, identifying feelings), and correcting normative beliefs (i.e., on the level of acceptance and use of substances among peers). It has to be delivered in an interactive way that engages young people. It is not yet fully understood which elements within social influence programs contribute most to behavior change. While the life skills (i.e., social, personal, and refusal skills) components are well known and have been well researched (Bühler 2008), the role of social norms (see Sect. 8.2.2) in the success of an intervention is only recently gaining the attention of researchers. Its premise is that overestimating the substance consumption among peers may lead young people to initiate or intensify consumption beyond their original intention. Such effects have been found in a range of other health and non-health behaviors. Evidence from trials mostly carried out in the USA but also in Australia and Europe suggests that the social norms approach is a new avenue for reducing substance-use-related harm (McAlaney et al. 2011). As part of the first European drug prevention trial, European Union Drug Abuse Prevention (EU-Dap) (Faggiano et al. 2010), a mediator analysis found that the level of normative beliefs (but not the level of social and personal skills) mediated the program's effect on cannabis use.

Martinus et al. (2012) tested the transferability of the "social norms" approach to a UK (Scottish) secondary school setting and found similar substantial misperceptions (i.e., overestimation) among secondary school pupils of their peers' drinking behavior when with friends.

Even if the effects of school-based prevention at the intervention level are often small, social influence programs can be an important mechanism for transmitting societal norms on substance use to young people. They can help them to further develop their skills to make and implement safer decisions about substance use or in situations where others are using. They also offer the potential of creating a more sympathetic environment for complementary systemic strategies, such as restrictions on advertising for legal psychotropic substances (Midford 2010).

8.2.4 Selective Prevention: Intervening with (Vulnerable) Groups

Selective prevention intervenes with specific groups, families, or communities that, mostly due to their limited social ties and resources, may be more likely to develop drug use or progress into dependency. Often, this higher vulnerability to problem drug use stems from social exclusion, lack of opportunities, and less-nurturing family or community environments. Therefore, European countries most frequently report

vulnerable groups as being young (drug law) offenders, youth in deprived neighborhood, homeless youth, some ethnic minorities and immigrant groups, school dropouts, students who are failing academically, and vulnerable families. These vulnerable groups are mostly identified using social, demographic, or environmental risk factors known to be associated with SUD. Targeted subgroups may be defined by family status or place of residence, such as living in deprived neighborhoods or areas with high drug use or trafficking. This means that prior to providing the intervention, the situation and vulnerability pattern of a given target group has to be studied. This clearly differs from universal prevention, where universal risk factors are addressed. Since this vulnerability assessment relies on social and demographic characteristics at the group level, individual risk cannot be assessed.

Implementing experimental evaluation designs with groups that are often hard to reach is extremely difficult and frequently impossible. For this reason, evidence for the effectiveness for selective prevention is currently limited. However, the American cross-site evaluation of interventions for high-risk youth, together with European (Jones et al. 2006; Roe and Becker 2005) and American (Hansen et al. 2007; Sussman et al. 2004) reviews of the evidence, allowed effective elements of such interventions with vulnerable populations to be identified.

Effective elements include changing access within the environment, promoting the development of personal and social skills, promoting positive relations in families, addressing social influences, providing social support and helping participants to develop goals and alternatives, developing positive schools, and enhancing motivation to avoid substance use (Hansen et al. 2007). The effective components in selective prevention – inside and outside school settings – seem to be virtually the same as in universal prevention. Interventions that do not solely address drug use, adapt to young people's experiences, and avoid rigid abstinence-oriented messages have proven to be more effective. They address social needs connected to drug use, rather than drug use behavior (Steiker 2008). After all, drug use in these populations should be considered as just one of several expressions of behavioral maladjustment. The specific challenge lies in targeting the right group with the right type of prevention intervention and delivering the effective components in appropriate ways. Vulnerable groups are often not so easily "available" as pupils in schools and typically do not approach public services.

In summary, prevention that targets vulnerable people may moderate the effect of an early developmental disadvantage, its translation into social marginalization, and progression into substance abuse. Several research studies have shown that interventions delivered during the early school years that aimed to improve educational environments and reduce social exclusion also had a moderating effect on later substance use (Toumbourou et al. 2007), without specifically targeting youth who experiment with drugs.

Although often unacknowledged, outcomes of the prevention programs described here can also be beneficial in behavioral domains beyond substance use, such as the prevention of violence, delinquency, academic failure, teenage pregnancies, and unprotected sex. Substance use prevention professionals are often unaware that smoking, drinking, safe sex, and healthy nutrition among adolescents

share common determinants. Recent empirical studies and reviews identified several common factors for all of them: beliefs about immediate gratification and social advantages, peer norms, peer and parental modelling, and refusal self-efficacy (Peters et al. 2009).

The prevention of different problem behaviors belongs to segregated political portfolios in most countries, and therefore a cohesive, coherent, and efficient approach to adolescent vulnerability is often lacking. In those few countries where such cohesive policy responses to multiple risk behaviors have emerged (e.g., the UK and North America), there is increasing evidence for the effectiveness of such integrated approaches. However, the implementation and evaluation of such interventions are causing complex challenges (Hale and Viner 2012).

Both professionals and policymakers in Europe have easily adopted the concept of selective prevention. Since universal prevention has been criticized as being abstinence focused and therefore inappropriate for young people's experiences (Skager 2007), many professionals began considering selective prevention as panacea and the "best fit" for European realities. Several researchers have, however, raised concerns regarding possible iatrogenic effects when vulnerable young people are grouped together in selective interventions. Problem behavior may get worse when members of this selective group model to each other's problem behavior ("deviance modelling"), thereby corroborating their belief that their deviant behavior is "normal" while the surrounding social environment is not ("norm narrowing"). Such iatrogenic effects are unlikely to occur in universal prevention, where some program evaluations in school and family settings (Koning et al. 2012) found that the more vulnerable subgroups within the universal target population benefited relatively more from the intervention, possibly because they adjusted their behavior to that of the "conventional" majority.

8.2.5 Family-Based Prevention: Universal and Selective

Many parents in the Western world tend to assume that a close, warm, and open relationship with their children is protective against SUD, by providing them with a space to test their own boundaries. Recent research has provided considerable support for the idea that not only parental support but also monitoring and control are strong determinants of lower prevalence levels of adolescent risk behavior.

There is now a plethora of studies on the relationship between parental styles and their offspring's drug use. They classify parental behavior on two axes, warm–distant and strict–lenient. Research indicates that the authoritative style (strict and warm) is the most protective against substance use, while the neglectful style (lenient and distant) increases the risk of drug use; research on the authoritarian and permissive styles is as yet inconclusive. Factors beyond parenting style, such as parents' drug use, emotional support and warmth, family structure, and influence of culture, need to be taken into consideration (Becoña et al. 2012).

For instance, Van der Vorst et al. (2006) suggest that clear rules about alcohol drinking in families are protective, while talking about alcohol and its risks proved

rather counterproductive. In a recent longitudinal study with over 1,400 students aged 14–20, high parental monitoring predicted significantly less use of alcohol, cocaine, prescription drugs, ecstasy, and drinking to intoxication, and this also applied for high-risk students in alternative curricula (Clark et al. 2012). A meta-analysis (Lac and Crano 2009) that assessed the perceptions of 35,367 adolescents (from 17 studies) of parental monitoring and linked it to their marijuana use found a strong protective effect ($r = 0.21$) of parental monitoring activities. The association was significantly stronger in females and even existed when parental monitoring was defined purely in terms of parental knowledge of the child's whereabouts, activities, and relations.

Monitoring and warmth together appear to predict adolescents' social and interpersonal perceptions of drug use and their actual drug use 1 year later (Hemovich et al. 2011), which reminds us again of the importance of adolescents' social and intrapersonal beliefs for their use of illicit substances. Results of studies on monitoring from before 2009 are difficult to include here, as they often measured parental knowledge instead of actual active parental monitoring (Racz and McMahon 2011).

A recent study in the Netherlands (De Looze et al. 2012) found that specific parental rules about smoking, drinking, and adolescent risk behavior were associated with a lower prevalence of the targeted behaviors (i.e., smoking and drinking). Independent of adolescent smoking and drinking behaviors, these parental rules on smoking also predicted lower prevalence of cannabis use and a lower rate of early sexual intercourse. This suggests that clear parental rule setting is more strongly related to lower levels of risk behaviors in adolescents than are more general parenting practices.

The findings give additional etiological underpinning to an intervention study that tested the Swedish Örebro program in the Netherlands. The program combines parent and student interventions and establishes simple drinking rules, coordinated between home and school, which had shown to be effective in most implementations in Sweden (Koutakis et al. 2008).

The program in the Dutch context (Koning et al. 2012) was only effective in preventing weekly drinking when family and school interventions were combined, and among those adolescents reported that they had lower self-control and more lenient parents at baseline. The mediators of these effects were clearer rules and attitudes in parents. It is interesting that a program that only requires, on the part of the school, a 15-min intervention at the regular parents' meeting at the beginning of the school year has relevant effects on self-control in adolescents and restrictive parenting.

Strict family rules about drinking were also tested against a (harm minimization) model according to which alcohol use is a part of normal adolescent development while parents should supervise their children's use to encourage responsible drinking. The study (McMorris et al. 2011) compared adolescent alcohol use and related harms among adolescents ($N = 1{,}945$; 989 females) in Washington State, USA, and Victoria, Australia, two states that have respectively adopted zero tolerance and harm minimization policies. Despite those differences, family context was related

to alcohol use and harmful use in a very similar way, but adult-supervised alcohol use resulted in higher levels of harmful alcohol consequences. This challenges the assumption that supervised alcohol use or early-age alcohol use would reduce the development of adolescent alcohol problems. Both Mediterranean drinking cultures and Danish drinking parties where parents organize and supervise alcohol consumption among their teenage offspring are based on this rationale. A large European study (Kuntsche and Kuendig 2006) confirmed that the perception of excessive drinking in a family is more closely related to both frequent and excessive drinking than to family structure, but family bonding was even more closely related than drinking perception. The findings underline – for European contexts – the importance of factors related to family life and support that minimize the risk of frequent and excessive drinking despite given risk factors (Kuntsche and Kuendig 2006).

In terms of prevention practice, the question again arises of how parental control, warmth, rules, and monitoring can be increased or strengthened by interventions and how these interventions should be delivered and to which families. The analysis by Hemovich et al. (2011), for example, found that single-parent families and those with lower incomes provided less monitoring, which was related to more drug use, but not less warmth. This leads back to the importance of distinguishing between universal family-based approaches that target all parents and those selective ones designed for the more vulnerable families that have fewer financial, personal, and time resources.

Most of the effective family-based programs contain elements of monitoring, rule-setting, and contingency management. Some of them – such as the Strengthening Families Program (SFP) – were originally designed for the most vulnerable families. In systematic reviews (Foxcroft and Tsertsvadze 2011b; Petrie et al. 2007), the SFP was considered effective in preventing substance use – including over the long term – and other problem behaviors. It seems to be the only program to demonstrate in randomized control trials improvements in the outcomes for the children, in addition to improved parenting skills and reductions in child maltreatment. Particularly, selective family-level interventions might not demonstrate benefits where they are applied more universally to include families with very low rates of problems at child or family level. However, addressing all families using a universal prevention approach might allow more vulnerable families to adopt educational, normative, and behavior models from the more conventional families in the same group, so that often the more vulnerable families profit most from such programs. Depending on how they are delivered, some universal programs might predominantly attract the well-off, low-risk families; however, effective (often selective) programs tackle this imbalance by offering transportation, child-care, and food at the venues – elements that might be essential for families in need.

A systematic review (Broening et al. 2012) of programs for substance-affected families found interventions to be effective when their duration was longer than 10 weeks and when they involved children's, parenting, and family skills training components. Proximal outcomes (e.g., knowledge, coping skills, family relations)

showed better results than more distal outcomes (e.g., self-worth and substance use initiation). Apart from a few studies, the long-term effects on young people's substance use, delinquency, mental health, physical health, and school performance have rarely been assessed in the evaluations.

The need to break intergenerational cycles of poor parenting practices was addressed by Hill et al. (2010), who examined the extent to which interactions between behavioral disinhibition, behavioral inhibition, and family management during adolescence (from age 10) predict alcohol abuse and alcohol dependence at age 27. Young people who were high in behavioral disinhibition were at increased risk of later alcohol abuse and dependence, but only in consistently poorly managed family environments, while in consistently well-managed families, high levels of behavioral disinhibition did not increase the risk of later alcohol abuse or dependence.

Overall, across universal and selective interventions, there is good evidence from Cochrane Reviews that family-based prevention interventions are effective in reducing young people's alcohol, tobacco, and drug use (Foxcroft and Tsertsvadze 2011a; Gates et al. 2007).

8.2.6 Indicated Prevention: Intervening with (Vulnerable) Individuals

Indicated prevention aims to identify individuals with behavioral or psychological problems that may be predictive of developing problem substance use later in life and to target them individually with special interventions. Indicators of increased risk can be dissocial behavior and early aggression as well as alienation from parents, school, and peer groups. The aim of indicated prevention is not necessarily to prevent substance use but to prevent or at least delay development of a dependence, to diminish the frequency and to prevent more risky patterns of substance use (e.g., moderate drinking instead of binge drinking). This European definition of indicated prevention differs slightly from the original definition by the Institute of Medicine (IOM) (Mrazek and Haggerty 1994), "to identify individuals who are exhibiting early signs of substance abuse (but not DSM-IV criteria for addiction) and other problem behavior and to target them with special interventions." "Early intervention" stands for a subgroup of measures of indicated prevention focusing only and specifically on identifying substance-using individuals to prevent them from progressing into problem drug use.

The IOM definition for indicated prevention has spread the notion that signs of problematic substance use would be the principal aspect we need to look at if we want to prevent SUD in vulnerable individuals. However, a considerable body of evidence (Glantz et al. 2009) suggests that a set of behavioral and mental problems and disorders with onset in early childhood significantly increase the propensity of affected children to develop SUD earlier or faster, once they have initiated substance use. These aspects of vulnerability at the individual level do not seem to be covered clearly enough by the IOM definition, and therefore, professionals tend to

ascribe even very personality-focused interventions like Preventure (see below) to selective prevention (Conrod et al. 2013).

The European definition considers problematic substance use to be one among the behavioral or mental health problems that lead to SUD, which can be diagnosed at the individual level. It thereby maintains the distinction between vulnerability at the group level (selective prevention) and vulnerability at the individual level (indicated prevention) as it was originally intended by Gordon (1983): "Selective measures are advisable for population subgroups distinguished by age, sex, occupation, or other evident characteristics, but who, on individual examination, are perfectly well. Indicated measures are those that should be applied only in the presence of a demonstrable condition that identifies the individual as being at higher than average risk for the future development of a disease." This distinction is highly relevant for practice and policy because vulnerabilities at the social (demographic) level, those at the individual (mental health) level, and those at the environmental level affect the pathways to substance use disorder in quite distinct ways (Sloboda et al. 2012), and the focus of the respective prevention strategies should match the kind of vulnerability of the target populations.

In the European Union, the term "early intervention" has been coined for those specific forms of indicated prevention that consider exclusively the level of drug use as a predictor for developing SUD and aim to intervene early in a drug use career. Even though this interpretation has somehow become established in European policy documents, the original and predominant use of this term in the scientific literature refers to intervening early in lifetime (i.e., first childhood) to prevent a range of behavioral problems in disadvantaged children (Guralnick 2008). Most of the interventions in this group can be described as brief interventions (BI), sometimes including elements of motivational interviewing (MI).

There are no systematic reviews or meta-analyses assessing the effectiveness of interventions that target individuals with behavioral or psychological problems independent of any substance use. Nevertheless, the few available single intervention studies in Europe tend to be better designed and to provide stronger outcomes than those in selective prevention.

For example, the indicated school-based program Preventure targets adolescents (aged 13–14) with specific personality risk factors for early onset substance use disorder and other risky behaviors, in only two sessions. Even when implemented by nonspecialists, participants showed a lower likelihood of later onset of drinking or a less-steep increase in consumption and binge drinking. Effects beyond substance use included reduced scores in depression, panic attacks, truancy, and shoplifting (Castellanos and Conrod 2006). For young alcohol drinkers at baseline, the findings suggest that only four to six young people need to be exposed to the intervention to prevent one from later taking up heavy drinking. This "number needed to treat" (NNT) is one of the most favorable found to date in prevention interventions. Coping Power, a program targeting young people aged 8–13 with disruptive behaviors in the Netherlands showed at follow-up better results for smoking and cannabis use compared to treatment as usual (Zonnevylle-Bender et al. 2007).

These findings again illustrate that contemporary prevention interventions go well beyond simply presenting abstinence-oriented messages. Carney and Myers (2012) assessed the effectiveness of "early interventions" for adolescent substance use and behavioral outcomes in a systematic review (nine studies) and found benefits in reducing substance use and improvements in associated behavioral outcomes with small but significant behavioral and drug use outcomes, especially for individual interventions with more than one session.

Brief interventions (BI) consist of one-to-one counselling sessions, sometimes including follow-up sessions, which are delivered by trained health and social workers to people who might be at risk because of their substance use. It involves a prior assessment of substance use problems. In reviews, BI were found to be effective when delivered in the primary healthcare system and colleges, as well as online or via computers. However, these positive findings currently only relate to alcohol.

Brief interventions usually contain elements of motivational interviewing (MI). MI is a nondirective interaction technique where active listening and feedback are used to support clients in making decisions, hence using their own motivational momentum to change behaviors and set goals regarding their substance use. Motivational interviewing alone can be effective in reducing drug use – even in a single session – as shown in reviews by McCambridge and Strang (2004), but the outcome seems to depend on the quality of its delivery (McCambridge et al. 2011). Also, a Cochrane Review (Smedslund et al. 2011) found significant effects of motivational interviewing in short- to midterm follow-ups and in comparison to nonintervention.

A study of nightlife settings from Florida (Kurtz et al. 2013) suggests that even simple assessment and feedback interviews can reduce substance use in club-goers, a phenomenon that has previously been found in emergency room interventions for alcohol drinkers and might be a promising technique to be applied in conjunction with pill testing services at nightlife events.

8.3 Conclusion

Prevention has developed and made some progress in recent years, but there is still quite a lot of room for improvement. Overall, universal prevention seems to be dominated by interventions that might attract public attention but are not likely to be effective in preventing drug use. Policy interest in selective prevention has increased in the same period, but this has not translated into more interventions for vulnerable youth or more evaluation research. Finally, there has been some recent interest in indicated prevention in Europe. Here, well-designed evaluation studies have taken place, but the intervention coverage as such is still limited to only a few countries. Too many prevention interventions continue to appeal to cognitive processes only, namely, information provision, regardless of the negative evidence that has been reported about such interventions.

With the arrival of the phenomenon of "legal highs" and continuously innovating synthetic psychoactive substances offered on a globalized market, this weakest

of all prevention paradigms has been revived, and once again decision makers seem to be convinced that prevention funds are best spent in detecting, assessing, and warning youth about the dangers of these new substances. Policymakers and professionals have only reluctantly begun to acknowledge that social norms and their perception (environmental prevention) as well as impulse control (indicated prevention) are powerful determinants of adolescent behavior. The potential for using emotional and unconscious processes in prevention is virtually unacknowledged, while implicit cognition is regularly used in advertisement and marketing in order to boost consumption. Reviews found the largest effect sizes in studies that assessed implicit semantic associations employed word association measures and focused on marijuana use, suggesting that implicit cognition is a reliable predictor of substance use (Rooke et al. 2008). Only a few prevention approaches, particularly in the alcohol field, use techniques that aim to reverse the influence of the abovementioned unconscious cues by attempts to change learned associations, attention biases, and implicit attitudes.

In terms of gender differences, a number of program evaluations found, overall, less or no effects for girls (Kumpfer et al. 2008; Poduska et al. 2008; Vigna-Taglianti et al. 2009). One possible explanation might be a lower vulnerability at baseline, which could also reflect the fact that neurobehavioral disinhibition is found more frequently in boys. Alternative hypotheses are that these interventions are less appealing to girls or that the timing of delivery with regard to their cognitive, social, and emotional development is less appropriate, since girls mature earlier (Vigna-Taglianti et al. 2009). Kelly et al. (2011) found that girls' alcohol use was – compared to boys – more influenced by high-risk peer networks, while parental disapproval was less protective for them, compared to boys. So girls who, overall, use psychoactive substances less and have fewer problems might also gain less from existing prevention programs.

Reflecting the criticism that prevention is only abstinence oriented and is inappropriate to contemporary youth's need to acquire risk competence, the term "risk reduction" has been coined as a viable alternative for vulnerable or drug-using youth, as an analogy to what harm reduction would be in relation to treatment. However, the evidence, intervention examples, and theoretical frameworks discussed in this chapter show that "risk reduction" is intrinsically included in all prevention measures. Most prevention intervention in fact do not simply strive for abstinence but try to delay initiation, achieve generally better behavioral control and adequate socialization, or avoid rapid escalation from experimental use into SUD or even addiction, hence reducing risk and harms. Risk reduction can hardly be seen as separated from prevention, while such "harm reduction" approaches within prevention might only be effective and acceptable when targeted at older adolescents (over the age of 14) but not for younger adolescents (Poulin and Nicholson 2005).

As described above, there are still a number of limitations in the evidence behind prevention interventions. Nevertheless, given the limited number of options available for tackling addiction problems, one cannot only rely on treatment and harm reduction. Recent discussions about "recovery," in particular, bring us back to approaches that target a life free from the negative impacts of addictive substances and behaviors.

While treatment is based on the informed consent of the treated person, prevention interventions are usually the result of a unilateral decision taken by experts or policymakers, based on their assumption that an intervention will have positive effects on the targeted person and/or the social environment. While parents and teachers might take such a decision "on behalf" of their children and pupils, for adult target groups the responsibility clearly lies with experts and policymakers. As has been shown for mass media campaigns, the question of responsibility and consent is not an academic one, as iatrogenic effects of preventive interventions are possible. It is crucial, therefore, that decision makers take a well-informed position on behalf of their citizens in such instances.

As has been seen, especially in selective and indicated prevention, there is a considerable overlap between treatment and prevention. In many cases prevention offers an improved understanding of an individual's situation, a self-examination, or test, which might lead to treatment. A good example of this is treatment programs for cannabis users offered via the Internet, which frequently start as self-tests and may end up with a one-to-one treatment arrangement. Motivational interviewing can be used as a tool helping to bridge the gap between prevention and treatment.

While prevention has been traditionally linked to school curricula, TV, and information campaigns, the range of media and approaches now available has widened considerably. Web series, avatars, contacts, and information provided via SMS or Twitter are no longer considered new approaches and have now become part of the toolbox for prevention specialists. At the same time – also based on neuropsychological findings – prevention has become more unified, and a number of problematic behaviors, including destructive and violent behavior, substance use, and pathological use of computer games and the Internet, are today targeted with the same interventions. The need for a strong evidence base, critical reflection of practice, and adequate training of the staff involved remains central to all these approaches.

As we have seen in various sections of this chapter, social norms have a strong influence on behavior, suggesting that the effect of informal social control and social sanctions (from family and peers) may be more important than the certainty and severity of formal sanctions. These examples illustrate that comprehensive prevention policies ought not only to address individual vulnerabilities and illicit drug use. Informal social norms have a major but largely underestimated influence on initiation and level of substance use and related behaviors.

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Regional and Cultural Aspects of Prevention

9

Roland Simon and Gregor Burkhart

Contents

Abstract

Drug use and prevention has to be understood within its cultural environment and conditions.

There is increasing evidence that cultural values, descriptive norms, and the social acceptability of use influence people's initiation into substance use and problem behavior directly as well as indirectly through parenting practices. It has been argued that especially inconsistency between parenting style and culture can cause harm to adolescents' mental health.

Cultural and contextual differences between regions can also affect the implementation, acceptance, and effectiveness of prevention interventions.

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The focus of prevention approaches has differed between Europe, North America, and other parts of the world in recent years. North America has in the past decade focused more on manualized substance use prevention programs. While this has not been the traditional approach in Europe, such programs have been successfully transferred and adapted to European environments, either in content (words, names, examples, and images) or in structure (organization, training, staff, time, and length of sessions). This approach should be pursued further, especially at a time when it is unlikely that substantial new investments in prevention research will be made.

9.1 Introduction

Burkhart and Simon (# in this publication #) have shown that collective behavior and perceived norms have a significant influence on substance use behavior. This has implication for interventions, their effectiveness, and cultural acceptance. Most universal and selective prevention strategies only target individual behavior and decision-making, putting the onus of responsibility for behavioral control entirely on the individual and disregarding the influence of network and collective behavior (Szmigin et al. 2011).

9.1.1 Culture and Substance Use

From an etiological perspective, there is increasing evidence that the perceived availability of substances, normative environmental aspects such as cultural values, descriptive norms, and the social acceptability of use influence people's initiation into substance use and problem behavior. Several longitudinal studies have confirmed that descriptive norms and the misperception of normality ("Everybody does it") are important predictors of tobacco smoking (Cunningham 2007), frequency of alcohol consumption, and readiness to take significant risks to use cannabis, alcohol, and tobacco (Olds et al. 2005). Kuntsche and Jordan (2006) confirmed that regular contact with substance-using peers strongly correlates with individual substance use. Students who saw other young people attending school while intoxicated with cannabis or taking cannabis on the school premises used more cannabis themselves and had more cannabis-using peers. Cannabis use in the school environment seems to create an atmosphere that favors cannabis use independent of whether students have cannabis-using peers. The authors suggest that schools should create an overarching environment of disapproval of cannabis use as an effective means of prevention.

Societal values and norms not only influence student and adolescent behavior, but they also guide parenting practices. For this reason, "contextual" rather than "universal" monitoring activities would probably be more appropriate in family-based programs. While families' concern for their offspring is universal, the level of individuation and autonomy varies between individuals and between cultures. Arab

societies, for example, tend to be more collective and authoritarian than Western societies, with higher levels of emotional and financial connectedness and sometimes collective monitoring alongside parental monitoring. This higher level of adolescent–family connectedness has been associated with better mental health among adolescents in eight Arab societies (Dwairy 2006), indicating that authoritarian parenting within an authoritarian culture does not harm adolescents' mental health as this would be the case within Western liberal societies. The authors hypothesize that it is the inconsistency between parenting style and culture that causes harm to adolescents' mental health. This suggests that education has to be understood within its cultural environment and conditions.

9.1.2 Implementation of Interventions and Cultural Conditions

From an intervention perspective, cultural and contextual differences between regions – sometimes going back over centuries – can affect the successful implementation, acceptance, and effectiveness of prevention interventions. Interventions therefore have to take account of the collective aspects of some of the behaviors they wish to address. For example, differences in culture, context, and history must be taken into account when adapting North American programs for use in Europe. Essential components of community prevention approaches that are present in self-governance cultures such as the USA might not exist to the required extent in countries with different political traditions. This might include factors such as defining community norms and rules, volunteering and citizen involvement, self-organization, and social control. Such differences in political traditions explain why "community-based prevention" is difficult to implement in many countries. In most of Europe, the concept has a different meaning from the USA and is used to describe the activities of municipal services or institutions in nonschool settings.

These differences are also reflected in how prevention policy is managed. While in Europe stricter tobacco control has sometimes even been denounced as "fascism" and alcohol control as the surrogate of Nordic Puritanism, other regions of the world do not seem to have such an aversion to social and market control; for example, alcohol has been banned in Brazilian football stadiums since 2003. A country's social norms can create more opportunities for environmental prevention strategies, and this seems unrelated to the level of "repression" in a country; for example, several Latin American countries, including Brazil, have decriminalized drug use.

9.2 International Perspectives and Trends

The following chapter presents an overview of recent developments and trends in preventive measures. While the focus is on Europe, North America and other parts of the world are also considered.

9.2.1 Mass Media Campaigns

Mass media campaigns continue to be popular both in the Americas and in Europe, although they are evaluated more often in the USA. However, over a third of European countries have reduced or abandoned mass media campaigns on illicit drugs because of concerns about possible iatrogenic effects of such interventions and a lack of funds to implement them. Some countries, such as Bulgaria, the Czech Republic, Italy, Spain, France, and Romania, still use local and national mass media campaigns. It is possible that mass media campaigns still have a wider role to play in comprehensive social marketing strategies, such as those trying to change social norms.

9.2.2 Environmental Prevention

Environmental prevention is a new concept in Europe, even though in German-speaking countries the corresponding term (*Verhältnisprävention*) has been in use for many years.

Since the introduction of the Irish smoking ban in 2004 (following the EU signing of the WHO Framework Convention on Tobacco Control in 2003), environmental prevention strategies to restrict tobacco advertising and places where smoking is allowed have rapidly gained momentum, and today, a majority of Member States have total smoking bans in public places (for details, see www.emcdda.europa.eu/prevention-profiles). Following these changes – and possibly also as a result of them – the prevalence of smoking has fallen (Spinney 2007), particularly among adolescent boys (Hublet et al. 2009).

Advances in the environmental prevention of alcohol use have been less visible. The EU Alcohol and Health Forum was set up, and in 2006, the EU alcohol strategy was launched requiring several environmental measures to be taken. The 2009 implementation report of the strategy still lists a greater number of persuasive approaches (such as campaigns) than environmental strategies (such as regulation, taxation, or legislation). However, there is a continuous trend towards establishing a minimum age of 18 for selling and serving alcohol. Within EU Member States, environmental prevention approaches in schools have expanded, and today, almost all of them report total smoking bans in all schools, and a majority of countries report full or extensive provision of drug policies in schools, i.e., rules on the use and sale of substances on school premises and procedures to deal with violations. At the community level, the provision of environmental strategies such as community prevention plans and cooperative prevention work between community agencies has increased steadily since 2004.

It has been argued that a range of social problems, including substance use, teenage pregnancy, and violence, are more prevalent in countries with high levels of social and health inequality (Wilkinson and Picket 2010). Many Scandinavian countries invest heavily in broader environmental policies that are geared towards increasing social inclusion at family, school, community, and society levels and

that work to reduce and maintain lower levels of drug use. Prevention programs and interventions targeting specific problems or drugs are less often used in these countries.

Guidelines for the creation of better environments in recreational settings, such as the "safer dancing" guidelines in the UK, were developed since the end of the 1990s as simple but important environmental prevention tools to reduce the occurrence of problems related to drugs and alcohol. They include access to free drinking water, rules on glassware, noise, and staff training. Additional elements are policies on and monitoring of interior space in respect of risky sexual or aggressive behavior, training staff for medical emergencies related to intoxicated patrons, and policies for serving alcohol and handling drug-related problems. The strategies that are applied in Sweden and the USA (Miller et al. 2009) add more repressive elements, such as monitoring interior space for drug use and drug-related problems, training staff to detect drug-impaired patrons, and excluding "problem" patrons (drug dealers, drug users, those carrying weapons). While between 2004 and 2009 the number of EU countries that reported the existence of such guidelines increased from 3 to 12, only half of them appeared to monitor and enforced their implementation. In practice, even free drinking water – a core requirement for safe clubbing to counter the effects of dehydration and high temperatures while dancing – was available in the majority of relevant nightclubs in only 11 EU countries (2009 data).

9.2.3 Universal Prevention

Of the four main drug prevention strategies in Europe, universal prevention predominates and is probably the most commonly implemented, particularly in schools and families. The objective of delivering prevention interventions of the best possible quality in the context of increased financial pressures due to the economic downturn in Europe has led some countries to focus on improving the quality of their prevention programs and professionals. The Czech Republic, for example, has centralized the government's prevention funds and has introduced Europe's first accreditation system, under which funding is available only to certified programs. The certification of professionals is designed to improve the quality of delivery and to ensure that public funds are spent efficiently.

In comparison with the Americas, very few countries in Europe have implemented "manualized" programs (with the program details published in a manual which facilitates implementation according to set standards and rules), even if most of the available evidence on school-based prevention originates from them. The manuals provide material and guidance for teachers and pupils on the content of each of the sessions, promote discussions, and enable implementation and behavioral changes to be evaluated. The most important program is Unplugged, the only multisite randomized controlled trial (RCT) on prevention in Europe to date. This comprehensive social influence program consists of twelve 1-h interactive sessions delivered by class teachers and has proven its effectiveness in

a cluster randomized trial involving 7,079 pupils aged 12–14 in seven European countries (www.eudap.net). Drunkenness and cannabis use showed reductions after six 6 and 18 months; there was a reduced prevalence of all behavioral outcomes related to problematic drug and alcohol use among boys, but not among girls (Faggiano et al. 2010). Participation in the program was associated with decreases in drunkenness, intention to get drunk, and alcohol-related problem behaviors among adolescents from a low socioeconomic level. After this first European multisite prevention trial, Unplugged was implemented in more eastern European and Asian countries, in some cases replicating the initial promising outcomes.

One unusual school-based prevention approach deserves special mention. The Good Behavior Game (GBG) is not a typical lessons-based classroom prevention program but rather a way of managing whole primary school classes during regular lessons and socializing children to be self-controlled, emphasizing the role of significant others (teachers and peers) in children's social adjustment in school. Divided into teams, children systematically learn over a period of one school year to respect basic class rules through a well-designed process providing team rewards for respecting rules. RCTs reported a beneficial impact up to the middle school years and even young adulthood. These effects included reductions in alcohol and drug dependency disorders; antisocial personality disorder; delinquency and imprisonment; regular smoking; suicidal ideation and attempts; use of services for behavioral, drug, emotional, and school learning problems; and risky sexual activity such as unprotected sex. Substances and substance use are not explicit themes in GBG; instead, it focuses on socialization, and the children themselves define the behaviors that will be rewarded. GBG has been or is being implemented in at least four EU Member States. In a similar modus operandi, the Smokefree Class competition is an evaluated and effective program implemented in some European countries that works predominantly by setting alternative peer norms about smoking and stimulates their reinforcement by the peers themselves, but without mentioning the dangers or risks of smoking.

While these are excellent examples of more developed concepts and their implementation in Europe, the everyday practice of universal prevention in European schools still seems to focus primarily on nonevidence-based components – information days about drugs, visits by police officers, lectures from experts or former drug addicts, and interventions providing information (with no skills training) on the risks of drugs. There has, though, been a slight increase in manualized multi-session programs like Unplugged. These include training in communication skills and in the ability to handle conflict, stress, and frustration. They also try to correct normative misperceptions about drug use. This area, called "normative education," is still quite underdeveloped despite positive evidence (Martinus et al. 2012; Sussman et al. 2004). Many other manualized programs, though, still have information provision as the key component, with frontal (as opposed to interactive) delivery.

9.2.4 Selective Prevention

Compared to other parts of the world, Europe seems to have invested much political effort in addressing the problems of vulnerable groups, and since 2004, an increasing number of EU Member States have indicated vulnerable groups as primary targets for prevention interventions. However, in real terms, the reported level of intervention provision has only increased for two subgroups: young offenders and pupils with academic and social problems. The latter might be due to some Member States shifting attention in general to young people with academic problems and school dropouts, who share many risk factors with problem drug users. Young offenders as a group are easy to identify, but interventions provided are often not appropriate for them. While almost all EU Member States offer alternatives to imprisonment or penal sanctions for underage drug law offenders, treatment is not particularly tailored for them. They may be treated alongside more problematic drug users and/or dealt with as though they are themselves problematic drug users, increasing the risk of further marginalization and deviant behavior. In many cases, more suitable interventions would have clear and structured protocols, be of adequate duration, and be provided in neutral settings. The manualized program for young offenders (FreD) takes this approach. Developed at the national level, it has been expanded to and adapted by one-third of EU Member States.

Some countries have reacted specifically to the increased vulnerability to drug use found among pupils in vocational schools, for example, with tailored programs to generally improve literacy and numeracy levels among disadvantaged students. At the community level, municipalities in northern Europe and in Italy aim to combine drug and alcohol policies, action plans, and youth work through binding cooperation agreements between local authorities and nongovernmental organizations. Combining norm-setting environments and individual counselling approaches in this way might avoid segregating vulnerable young people into specific interventions for high-risk youth, which has the potential to cause further harm, as described above. Municipalities have closer contact with citizens and can better coordinate the different services involved. The strengthening of local responsibility for prevention has fostered community plans and interagency work, particularly in northern European countries.

Early intervention approaches, in the original meaning of the term, provide social, emotional, and learning support to children in the early years of life (this is distinct from the recent use of the term "early intervention" to mean "early in the career of substance use"; see below). It can delay or prevent future problems (including substance misuse) more effectively and economically than intervening only when problems appear. Parenting programs at a local level would be an essential part of early intervention, but proactive parental work and training is still an exception.

The content of interventions presented as "selective prevention" is often unclear, and problems in defining the scope of the concept make monitoring difficult.

The effectiveness of prevention is substantially affected by whether evidence-based (Sussman et al. 2004) elements – motivation, skills, and decision-making – are included or if there is just a distribution of, for example, information leaflets about drug taking, as some countries' data suggests.

Finally, the problem of delivery seems to be very relevant. In roughly two-thirds of EU Member States selective prevention is carried out by the many existing services and offices for youth, families, migrants, etc., usually via meetings with their clients at a service's office ("come structure"). Outreach work ("go structure") may be able to reach a wider group of people in need, but while outreach work as such is definitively well developed in Europe, it does not seem to be the main channel for approaching and engaging with vulnerable young people in selective prevention interventions.

9.2.5 Family-Based Prevention

Family-based prevention is widely utilized in universal prevention, but despite a lack of evidence about this approach, it seems to be mainly focused on providing information. Intensive coaching and training of families, an approach that has shown consistent efficacy across studies (Petrie et al. 2007), is provided in less than a third of EU countries. Very few countries report on more sophisticated interventions such as parents' peer-to-peer groups, personal and social competence trainings, or manualized parenting programs, although the number of countries using these types of intervention is increasing. There has been a general increase in the use of selective approaches targeting only vulnerable families, most notably families with substance use and who are socially disadvantaged. This might be related to the increasing popularity in Europe of the Strengthening Families Programme (SFP), a prevention program for parents and children in high-risk families that includes elements of parenting skills training, children's life skills training, and family life skills training. Outcomes include increased family strengths and resilience and reduced risk factors for problem behaviors in high-risk children, including behavioral, emotional, academic, and social problems, as well as reductions in substance use, conduct disorders, aggression, violence, and juvenile delinquency.

A practical problem is that many parents cannot be reached using the classic instruments of work with parents, such as parents' evenings or invitations for a talk during office hours. Interventions in Denmark, Germany, Italy, and Austria (e.g., Family Ties, www.familienbande.cc) aim to increase the parenting skills of parents and other adults involved in bringing up children and help them to develop responsibility and decision-making skills. The approach has made it possible to reach families with migration backgrounds as well as socially disadvantaged families. Special networks of counselling centers have been set up (e.g., in Germany and France) to provide concrete advice to families about how to deal with children who are using drugs.

9.2.6 Indicated Prevention

Children with behavioral disorders, such as coexisting attention deficit (hyperactivity) disorder and conduct disorder, are at a particularly high risk of developing substance use problems later in life (Szobot et al. 2007). Intervening with these children requires close cross-sector cooperation at the community level between medical, social, and youth services, from childhood on. This is rarely achieved, except in some isolated examples that combine counselling for parents and carers with concurrent medical, psychotherapeutic, psychosocial, and educational support.

In 2004, the concept of indicated prevention was practically unknown in Europe, with only Germany and Italy reporting measures for children with behavioral disorders. In 2010, some 14 Member States reported various forms of indicated prevention, the majority of which were "early intervention" and counselling for drug users; interventions for early onset behavioral problems were much less frequent. In 2012, few countries reported the use of structured or manualized interventions for such problems.

The school setting has become crucial for identifying vulnerable children and adolescents. In 2004, five EU Member States reported full or extensive availability of early identification of pupils with behavioral or drug-related problems, and this had increased to 11 in 2010. However, it remains unclear (i) whether this assessment is limited to drug-related problems or to a broader array of behavior problems and (ii) what actually happens once a pupil has been identified as being at a particular risk. While interventions for young people with behavioral problems as such are rare in Europe, specific indicated prevention that focuses on young people with problematic substance use is much more frequent. A quarter of Germany's registered prevention interventions are this type of "early intervention," and in France, prevention seems generally to be conceived in this way.

Unlike adult drinkers who request primary health or emergency services, young alcohol or drug users feel healthy and mostly have no self-perception of problems. Screening and assessing them for possible problems is therefore a particular challenge. In Europe, drug tests are very rarely used for assessing drug-related problems in pupils (under suspicion), and often tests are not allowed; in the USA, by contrast, even random drug tests seem to be common (Ringwalt et al. 2008). Even in those few countries (the UK, Finland, Croatia) where confirmatory drug testing in schools is legally allowed, it is seldom used.

Once a pupil has been identified as a problem or risky drug user, referral to treatment and counselling centers seems to be common, while interventions for drug-using pupils within the school itself are found in only a few countries. SKOLL (www.skoll.de), a 10-week program of training in self-control for young people with risky substance use, was implemented nationwide in Germany at schools and in other settings. Its evaluation showed that the participants had reduced drug use and risky behaviors over the course of several months, and at the same time, they developed more self-confidence, alternatives to risky behavior, and social contacts. Those young people who were more vulnerable benefited most. SKOLL has been

continued, is used to supplement existing interventions, and is especially attractive for sparsely populated areas as provision through the school environment allows regular access to all children at that age. France has set up special cannabis counselling centers in many cities.

Brief Interventions programs have been implemented in a small number of European countries, targeting mostly alcohol users in primary healthcare or emergency room settings (www.esbirtes.eu). Brief Interventions with elements of Motivational Interviewing are occasionally used to target young people and their cannabis use in street-work setting. While these interventions have not been reported in schools in the EU, in US schools, in comparison, Brief Interventions have been used fairly frequently (Winters et al. 2012).

Brief Intervention with elements of Motivational Interviewing is delivered both face-to-face and via interactive counselling websites in an increasing number of countries. Telephone helplines and SMS-based programs – often linked with these websites – aim to provide similar services. Since "early intervention" relies on detection and proper assessment of potentially harmful substance use, its implementation beyond schools, primary care (alcohol), and emergency services is a challenge. The advantage of the Internet-based approaches – especially when they address illicit drugs – is that they guarantee their users' anonymity and might attract substance users who would not approach any regular assessment or counselling service.

Indicated prevention could reduce the negative impact of neurobehavioral problems, such as early aggression on later substance use, and other problem behavior from childhood on. This possibility still seems to be largely ignored in Europe, where some prevention professionals reject the approach as being a "medicalization" of educational problems because it is based on neurobiological and neuropsychological findings (e.g., Sloboda et al. 2012).

9.3 Transfer of Prevention Technologies

Prevention research in North America is generally more developed than in Europe. This is related to structural differences in social policies and prevention practice as well as to research funding. In the European Union services such as healthcare and education are generally of quite a high quality and are widely available, which is not the case in most other regions of the world. As a consequence, in these regions, prevention programs are developed or used to promptly address a range of emerging social problems; this approach might hence be a consequence of a lower availability of universal social, youth, and health services.

The evidence for the effectiveness of substance use disorder prevention comes almost exclusively from evaluations of sophisticated manualized programs (Bühler and Kröger 2008; Faggiano et al. 2008; Foxcroft and Tsertsvadze 2011a, b, c; Gates et al. 2007), but these programs require considerable investment and incur high developmental costs. Given the structural differences described above, this is a more common approach to prevention in North America. Investment in research

and tools helps to improve prevention interventions and to assure their effectiveness in replication trials, as well as making them easy to apply. Their implementation is more likely to be set out in a manual (i.e., manualized) to assure accuracy of implementation and to allow trained staff who may not be prevention experts to implement them. Such programs are also more likely to have been pretested (to confirm the validity of their theory base), to have been checked for unintentional (iatrogenic) effects, and to prove positive outcomes. Such interventions could be considered "high-tech prevention," as their development and partly also their implementation require specific know-how, research, repeated refinement procedures, quality control, proof of effectiveness, replication studies, and some certainty that they do not harm. In medicine, most people would naturally expect such a level of "technology assessment," especially of medications, before they can be distributed to the population.

In Europe such high-tech programs are rare, especially outside classrooms. Prevention strategies mainly consist of varying combinations of policies for vulnerable populations; isolated or combined activities for school-aged youth to raise their awareness, self-competence, social skills, risk perception, and/or autonomy; events and advice for parents; and youth work and counselling interventions for those with existing risky substance use patterns. Such approaches have to make use of the existing services and infrastructure, and they allow for innovation and adaption to local needs and perceptions. However, they are sometimes based on little more than common sense and often lack evidence of both effectiveness and possible iatrogenic effects. While Europe has a range of innovative and pragmatic selective prevention interventions for vulnerable groups, many of them are not rigorously evaluated. Few indicated prevention programs are running, even though some well-evaluated and effective programs exist.

In broad terms, it seems that the relative lack of prevention infrastructure in the USA has led to more prevention research and program development. Europe, on the other hand, relies on a more elaborate infrastructure but spends much less energy on ensuring that the many different existing services deliver prevention work of a specific quality. However, there are examples in Europe that do control the quality of programs. In the Czech Republic, quality control is carried out through an accreditation system and through regulating training of the professionals involved. Recently developed European drug prevention quality standards might help to steer prevention policies in the EU as a whole in new directions.

9.3.1 Examples of Successful Transfer

Well-developed programs from North America have been culturally adapted to suit other parts of the world. Using a preexisting program means that the resources, manuals, and methodologies are ready for immediate use, facilitating implementation.

However, in Europe, there has been an aversion to the standardization inherent in manualized interventions and a belief that cultural and organizational differences between North America and Europe would make the adaptation problematic. Some problems seem to be real: (i) evidence-based programs from North America are often more demanding and complex than European interventions, which tend to be shorter, simpler, and more flexible, and (ii) North America has a long history of community mobilization and commitment to address problems from the bottom up. Europeans tend to have a state-oriented focus and generally believe that social problems should be addressed by service provision. Citizens in some regions outside the EU appear to see the state as having a reduced role and therefore have fewer expectations of state provision. This may be why countries in Latin America and in Asia do not appear to have many problems in adopting and adapting evidence-based programs from other parts of the world.

Despite the difficulties and hesitations described above, in the past decade, a number of manualized substance use prevention programs from North America have been successfully transferred and adapted to European environments, either in content (words, names, examples, and images) or in structure (organization, training, staff, time, and length of sessions). The most relevant examples are as follows:

- Preventure (Conrod et al. 2013), an indicated program in school settings for sensation-seeking young alcohol drinkers, developed in Canada, is currently being implemented in the Czech Republic, the Netherlands, and the UK.
- The Good Behavior Game (GBG) (Kellam et al. 2011), a universal classroom-based program that sets and reinforces simple behavioral norms, has been implemented in Belgium and is currently being implemented in the Netherlands, Slovenia, and the UK.
- The Strengthening Families Program (SFP), originally a selective family-based program first developed in 1983 in Utah in the USA (Kumpfer et al. 2012), was revised in 1992 into a shorter (and more universal) version (Molgaard et al. 2000), the Iowa SFP. Versions of the SFP are currently being implemented in Germany, Ireland, Greece, Spain, the Netherlands, Austria, Poland, Portugal, Slovenia, Sweden, and the UK.
- Communities That Care (CTC), a community empowerment and planning approach that includes a set of universal and selective interventions to be implemented in and with communities, was developed (Hawkins et al. 2008) in Seattle, Washington, and is currently being implemented in Germany, the Netherlands, Sweden, and Croatia.

It has become clear from the publications and experiences of the implementers and evaluators of those programs in at least 12 EU Member States that adaptation and implementation were both feasible and effective (where outcomes are available). While a considerable amount of time and effort was spent preparing, pretesting, and consulting with the target populations in order to adjust the programs to culture and context, in most cases, it was preferable to adapt an available effective program than to develop a new one from scratch.

9.3.2 The Role of Social Capital

Professionals who intend to transfer prevention technologies between different contexts might need to examine social capital levels in each context. While social capital is a product of both social history (context) and traditional values (culture) and is outside the immediate influence sphere of prevention programs or policies, it defines the setting in which an intervention is going to be implemented. In areas with higher social capital, networks of trust make it easier for programs to be implemented and enable resources to be better used. In societies with lower social capital, where community involvement is low, family-based prevention programs, for example, might encounter more difficulties.

As Fukuyama (2001, p. 18) argues, "the greatest direct ability to generate social capital is education. Educational institutions do not simply transmit human capital; they also pass on social capital in the form of social rules and norms." By the same line of reasoning, prevention programs are an important mechanism for transmitting societal norms (Midford 2010). If prevention programs manage to increase the cooperation of community agencies and families, social cohesion might grow as a consequence of program implementation. Such cultural and structural differences have also influenced the advancement of environmental prevention in different regions. We have argued that environmental prevention has gained momentum in most European countries in the last few years in relation to tobacco, but remains unpopular in relation to other aspects, such as alcohol and nightlife settings. Also in the USA, tobacco legislation is not homogeneously and rigorously implemented (see http://www.stateoftobaccocontrol.org/state-grades/state-rankings/smokefree-air-laws.html), and the USA has not signed WHO's Framework Convention on Tobacco Control. However, strong tobacco control policies and social norms against smoking were already well established in Canada and many Latin American countries before Europe began implementing tobacco legislation in 2004. This is one factor contributing to the lower smoking prevalence found in many Latin American countries compared to Europe (Eriksen et al. 2012).

9.4 Conclusion

Cultural and contextual differences between regions – sometimes stemming from old historical roots – can affect the implementation, acceptance, and effectiveness of prevention interventions. Interventions therefore have to take account of the collective aspects of some of the behaviors they address. Culture influences drug use behavior directly, but also indirectly, for example, through differences in education and parenting.

Prevention in Europe has developed and made some progress in recent years, but the situation is still far from perfect. Overall, universal prevention seems to be dominated by interventions that might get the public's attention, but are most likely

not effective in preventing drug use. Interest in selective prevention has increased during this period, but this has not translated into more interventions for vulnerable youth or more evaluation research. Finally, there has been some interest in indicated prevention in Europe, and effective evaluation studies have been carried out, but these types of intervention are still limited to only a few countries. Too much prevention in Europe and seemingly elsewhere – apart from North America – continues to appeal to cognitive processes only, namely, information provision. And too often interventions only target individual behavior, ignoring the fact that it is culturally embedded.

Findings from country-level ecological analyses on the health of young people (Viner et al. 2012) show that the strongest determinants of adolescent health worldwide are structural factors such as national wealth, income inequality, and access to education. As a consequence, safe and supportive families and schools, together with positive and supportive peers, are crucial in addressing risk and building protective factors. These are not limited to the neurobiological factors outlined at the beginning – childhood trajectories towards health and well-being are also modified by economic and social factors within countries, leading to inequalities. But there is evidence that effective prevention programs can reduce the effects of social inequality on behavioral outcomes. In fact, some universal prevention programs have shown differentially better effects on more vulnerable children (Kellam et al. 2008); some selective family-based programs seem to be more effective the more vulnerable the targeted families are (Kumpfer et al. 2008); and indicated programs can bring the most behaviorally difficult children to better social functioning. Most importantly, almost all interventions have positive spin-off effects beyond substance use disorder on aggressive behavior and on mental health. Despite this, these tools are still underused.

As we have seen at various parts of this chapter, social norms have a strong influence on behavior, suggesting that the effect of informal social control and social sanctions (from family and peers) may be more important than the certainty and severity of formal sanctions (Paternoster 1987). These examples illustrate that comprehensive prevention policies ought not only to address individual vulnerabilities and illicit drug use. Informal social norms have a major but largely underestimated influence on initiation and level of substance use and related behaviors.

There is a limited number of prevention programs with well-proven evidence of effectiveness that are relatively easy to implement through manuals and other supporting materials. Better use could be made of these interventions, which have often been developed in North America. A number of successful examples have shown that this approach is worthwhile and promising. While cultural conditions cannot be ignored, it is possible to successfully adapt programs developed in one cultural environment to another culture. This approach should be pursued further, especially at a time when it is unlikely that substantial new investments in prevention research will be made.

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Section II

Screening and Early Interventions

John B. Saunders and Noeline C. Latt

Screening and Early Interventions: An Introduction

10

John B. Saunders and Noeline C. Latt

Abstract

This introduction describes the chapters published in Sect. II on "Diagnosis, Detection and Early Intervention for Substance Use Disorders". The first chapter provides an overview of the hierarchy of diagnoses employed in the substance use disorders field and presents the diagnostic criteria for the central disorders of repetitive substance use. Following this there are two chapters on screening tools and brief intervention approaches for alcohol use disorders and drug (including nicotine) use disorders respectively. A detailed literature review on early and brief interventions of substance use disorders follows. The final two chapters are concerned with biological markers of alcohol and laboratory techniques for identification of drug use respectively.

This section is concerned with the diagnoses that apply to substance use disorders and how these disorders can be identified at an earlier or milder stage and appropriate advice and treatment provided. The aim of early detection and brief intervention is to both reduce harm that would otherwise occur were substance use to continue unchecked and to prevent the progression to substance dependence (addiction) which would otherwise be a likely consequence of continued use.

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Current definitions and diagnostic criteria for substance use disorders form the opening chapter of this section. Written by John Saunders and Noeline Latt, the chapter begins with a reflection on the importance of a common language by which human disorders and problems can be communicated amongst addiction specialists and other health professionals and in a way that can be understood and appreciated by patients with these disorders. A historical review of the various concepts of substance use and its disorders follows. It will be seen that many different concepts have been promoted over recent human history and by different professional groups. Some of the concepts and definitions disagree as to the nature and also etiology of substance use problems, and these competing concepts are reviewed to provide a background to currently employed diagnoses.

A key development was the description, based on detailed clinical investigations, of the substance dependence syndrome by Edwards and Gross (1976). This concept initially applied to the alcohol dependence syndrome and has been subsequently accepted as the core syndrome for nearly all types of psychoactive substance that have abuse and addictive potential. The substance dependence syndrome is an atheoretical and non-etiological concept, purely descriptive but emphasizing the essential syndromal nature of substance dependence in which clusters of symptoms, experiences, and physiological features tend to occur in combination with each other in the affected person at around the same time and repeatedly so.

The substance dependence syndrome has been powerfully influential. It was the basis for the definitions and diagnostic criteria for substance dependence in two successive versions of the Diagnostic and Statistical Manual of Mental and Behavioral Disorders of the American Psychiatric Association, namely, DSM-IIIR (published in 1987) and DSM-IV (published in 1994). It also forms the basis for the understanding of substance use disorders amongst the literature developed by the World Health Organization, including the 10th revision of the International Classification of Diseases, ICD 10. Rather surprisingly, the concept of dependence has been aggregated with that of substance abuse in the latest DSM revision, DSM-5. The central diagnosis in DSM-5 of substance use disorder is a looser rather disaggregated concept, and although empirically based on questionnaire data, its value to guide clinical practice remains to be established.

Comprehensive clinical assessment of substance use disorders, with a particular emphasis on alcohol, is a subject of the following chapter by Teresa Bobes-Bascáran (► Chap. 14, “Clinical Assessment of Alcohol Use Disorders”). Clinical assessment of substance use disorders, like that in most medical practice, is based primarily on the clinical interview, supplemented by findings on observation and examination and importantly in many cases of substance dependence on collateral and corroborative information. Clinical assessment is also complemented by results from laboratory tests, but these are the subjects of two separate chapters in this section.

This second chapter outlines the areas necessary for exploration in the clinical interview, including the (i) assessment of the use (intake) of the particular

substance, (ii) substance-related behaviors particularly those that might reflect dependence on the substance, and (iii) the range of harms arising from substance use, be they medical, traumatic, neurocognitive, psychiatric, social, or legal. Several tables summarizing key domains for enquiry are included in this chapter.

Screening and brief intervention for alcohol use disorders has been the subject of much emphasis since the mid-1980s. This followed reviews conducted by the World Health Organization, The Institute of Medicine, and many national and professional authorities which emphasized that it was inadequate merely to provide treatment for people with established dependence and late stage and often irreversible complications. Far better to identify an alcohol use disorder at an earlier or milder stage of its development, which it would be termed hazardous alcohol use, harmful alcohol use, or alcohol abuse, when the person affected would not have the physiological changes of a dependence syndrome and would be better able to modify their use and at a change when their life generally was more likely to be intact. The empirical evidence for screening and brief intervention for alcohol use disorders is compelling. Scores of randomized controlled trials and met analyses have shown evidence for effectiveness of this approach, although the overall effect size is modest. The real advantage of screening and brief intervention is that it can be offered at the point of first contact with the health care system, it can be repeated as appropriate, and – a more recent development – it can be presented electronically in a way which is confidential and engages the person with the substance disorder.

This chapter, written by John Saunders and Noeline Latt, reviews the available screening instruments for alcohol use disorders with an emphasis on the modern generation of instruments such as the Alcohol Use Disorders Identification Test (AUDIT). There follows a summary of the available data on the effectiveness of brief therapeutic interventions for alcohol use disorders, which typically but not necessarily follow a screening process. Evidence is provided for a significant reduction in alcohol intake, frequency of drinking to impairment, alcohol-related injuries, and other problems and even in one analysis long-term mortality. The authors emphasize that the key issue for the screening and brief intervention approach in clinical practice is to provide incentives in the health care system for practitioners and also health care services to deliver these interventions in a systematic way. In an effort to provide greater reach to persons with substance use disorders, screening and intervention has been adapted to various types of electronic format, including computer-presented and website-based interventions which offer a high level of interaction and tailor-made advice.

Screening and early detection has also been adapted for other substance use disorders. With the expanding evidence on the adverse health effects of tobacco smoking, notably carcinoma of the bronchus, chronic obstructive airways disease, and accelerated vascular disease, public health approaches were established, initially in some English-speaking countries and Nordic countries to reduce cigarette smoking at a population level. In addition to public policies to discourage the uptake of smoking and the application of sales taxes to reduce the level of use,

programs of screening for cigarette smoking and nicotine dependence, combined with brief "quit smoking" interventions, were developed. The chapter by Sawitri Assanangkornchai and Guy Edwards reviews the commonly used screening instruments, including the various forms of the Fagerstrom questionnaire and also briefly the evidence for the effectiveness of brief smoking cessation techniques (▶ Chap. 13, "Screening for Nicotine and Drug Use Disorders").

The authors follow with a review of approaches for screening and early detection of drug use, including cannabis (marijuana), amphetamines, cocaine, and other psychostimulants and heroin and related opioids. They describe a purpose designed screening questionnaire developed as part of a World Health Organization collaborative study, the Alcohol and Other Substances Screening and Identification Test (the ASSIST). They review the utility of this instrument, both within formal screening programs and as a tool for early detection in clinical practice. Screening with the ASSIST leads conveniently to a brief intervention, and the format of the ASSIST initially identifies which substance is of most concern to the respondent. The therapeutic intervention then focuses on the nominated substance with the aim of cessation or minimization of use of that substance. The principle of adjunctive behavior also facilitates reduction of other unhealthy forms of substance use by that person.

The range of brief interventions currently available for drug use disorders is reviewed by Jennifer Harland and Linda Gowing. They examine the evidence for effectiveness of brief interventions as applied to the main forms of psychoactive substance use, namely, cannabis, psychostimulants, and opioids. Several controlled trials have shown that brief structured intervention can reduce the use of cannabis. The interventions tend to be lengthier and more intensive than the brief interventions described earlier for alcohol and cigarettes. With regard to cannabis, between one and four sessions each lasting for up to 1 h have been shown to lead to a significant reduction in cannabis smoking in a dose-dependent manner. These interventions represent the most effective ones to help people cease cannabis use, and the main question is how they might best be offered in health care systems. They are clearly too lengthy to be offered by general medical practitioners. Potentially, primary health care could be a suitable venue and with the involvement of a therapist to undertake the necessary screening and intervention. Other forms of drug use are less common in the general population, and the issue here is how brief interventions might be adapted for these forms of drug use and presented to populations at risk. We certainly have evidence for effectiveness of brief structured interventions aimed at cessation or reduction in psychostimulant use. Studies have shown that between one and six therapy sessions lead to an overall reduction in methamphetamine use by approximately 40 %. Similar findings are seen with cocaine-related therapies. As with cannabis these interventions tend to be lengthier, taking up to 1 h per session and are therefore out of the scope of general medical practice. Again, primary care settings could for a venue for these interventions to be provided by specific therapists.

The final two chapters in this section concern laboratory testing for alcohol and other drugs. Friedrich Wurst reviews laboratory tests of alcohol consumption, with

an emphasis on a new range of markers which represent intermediary metabolic products of alcohol. These include ethyl esters such as ethyl sulfate and ethyl glucuronide. Contrast is made between the existing conventional biological markers of alcohol and these new ones. The conventional markers reflect the pathophysiological effects of alcohol, particularly in excessive amounts on various organs and body systems. For example, alcohol-related bone marrow toxicity results in abnormalities of various indices in the full blood count, notably an increase in mean erythrocyte cell volume (MCV). Enlarged red cells are produced by bone marrow and persist for the typical length of a red blood cell, which is 4 months. The MCV can therefore provide a useful indicator of alcohol consumption in recent months, and, with the turnover of red cells, abstinence or substantial reduction in alcohol intake results in a gradual reduction in MCV. There is a range of liver function tests which can also reflect hepatic enzyme induction or hepatotoxic effects of alcohol. These include the transaminases, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), and gamma glutamyl transferase (GGT). Other liver function tests are affected by alcohol, but these, especially GGT, are the more sensitive markers. However, it will be apparent that other causes of liver disease, unrelated to alcohol, can cause abnormalities, as indeed can certain diseases of muscle and bone where these enzymes are also present. Other biological markers of alcohol that have been employed include uric acid, HDL cholesterol, and urinary metabolites such as 5-hydroxy tryptophol. As Dr Wurst indicates, the particular advantage of the ethyl esters and related compounds is their greater specificity for excessive alcohol consumption. These markers are still in the research phase, but their potential may well be realized for clinical and population-level screening.

The final chapter in this section covers laboratory testing for drugs and is written by Philip Paull. In contrast to the laboratory markers for alcohol, detection of drug use involves identification in urine, blood, saliva, or other body fluids of the parent drug or a metabolite. Equivalent biological markers of drug use (to those available for alcohol) do not exist. Paull reviews the currently available assay systems for drug detection. Broadly, they encompass screening tests, several of which can be undertaken in hospital wards, clinics, and consulting rooms. More definitive assays are undertaken in specialist drug testing laboratories, and in addition to various screening tests based on electrophoresis and radio immunoassay, definitive identification of the specific substances is also available using gas chromatography combined with mass spectroscopy (GCMS). This technique is based on a unique signal that different chemical compounds produce in terms of the mass ratio at a particular point in the spectrum. There is increasing emphasis on drug screening which can be undertaken in clinic settings. This is particularly valuable when decisions on treatment or the application of contingencies has to be made when the drug user is attending for therapy. The ability to provide feedback within a short period of time based on the presence or absence of a particular drug is a considerable advantage compared with the time that is commonly taken for a urine (or other) sample to be delivered to a laboratory, for the assay to be undertaken, and the result returned to the requesting practitioner.

In summary, the chapters in Sect. II provide a state-of-the-art account of methods of screening and brief focused interventions, with the first chapter on "Diagnosis and classification" (▶ Chap. 11, "Diagnostic Definitions, Criteria and Classification of Substance Use Disorders") providing a clear categorization of the various types of drug-related disorder that are the target of these interventions.

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Diagnostic Definitions, Criteria and Classification of Substance Use Disorders

11

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Abstract

Diagnostic terms exist to identify forms of substance use which are causing clinical impairment or risk and to distinguish them from normality. Acute intoxication refers to a state caused by the acute pharmacological effects of the substance. Repetitive substance use which confers the risk of harmful consequences is termed "hazardous" or "risky" use. Substance abuse is a DSM-IV term which denotes a maladaptive and repetitive pattern of substance use which causes essentially social and personal problems. "Harmful use" is an ICD-10 term which denotes repetitive substance use which is actually causing physical or psychiatric harm. At the top of the hierarchy of disorders in both DSM-IV and ICD-10 is the substance dependence syndrome. This is defined as a psychobiological syndrome that comprises impaired control over substance use, tolerance, and withdrawal symptoms and is characterized by continued use of the substance despite harmful consequences. Underlying the dependence syndrome is a set of enduring neurobiological changes in brain reward, stress, salience, and control systems. These result in an internal "driving force" to use and continue to use a particular substance (or group of substances) in a self-perpetuating way. The recently published DSM-5 has changed the diagnostic landscape as it has deleted the diagnoses of substance dependence and substance abuse and replaced them with a broader condition of "substance use disorder." DSM-5 also classifies as "substance-induced disorders" the conditions of intoxication and withdrawal. In addition to these diagnoses are the numerous mental, neurocognitive, and physical complications. They include substance-induced mental disorders such as depressive disorders, anxiety disorders, psychotic disorders, bipolar and related disorders, obsessive–compulsive and related disorders, sleep disorders, sexual dysfunctions, delirium, and neurocognitive disorders. ICD-10 has comprehensive coverage of all physical disorders induced by psychoactive substance use. However, DSM-5 essentially neglects the significant medical/physical complications of alcohol and other substance use and has abandoned the multiaxial system, which included (as Axis III) associated physical conditions.

Diagnosis is based on a set of specific diagnostic criteria which reflect the particular pattern of substance use and the psychophysiological attributes and mental and other consequences of the condition. The key diagnoses in DSM-IV, DSM-5, and ICD-10 are reviewed in this chapter. Clinical diagnosis of these disorders is based on clinical knowledge and training. In addition there are several diagnostic interview schedules, together with screening and assessment instruments, which contribute to the diagnosis.

11.1 Introduction

Psychoactive substance use exists as a continuum and substance use disorders as a hierarchy. Some forms of substance use, for example, alcohol, are not harmful, or at least very low risk, in small amounts. Other psychoactive substances such as prescribed benzodiazepines are medically necessary and appropriate in many

situations. Illicit drugs, such as cannabis (marijuana), may have functional value to some people, and there may be a threshold of use for some beneath which little harm occurs. However, all these substances have an inherent capacity to cause intoxicating effects, dependence (addiction), and a range of physical, neurocognitive, psychological, and social harms.

Diagnoses are made to facilitate communication between different health-care providers and to provide a basis for some form of intervention. The intellectual process underlying diagnosis also serves to distinguish the patient's condition from normality. Some diagnoses indicate forms of substance use that confer the risk of harmful consequences in the future, others indicate current clinical illness or impairment, and yet others indicate syndromal disorders. A coherent system of diagnosis and classification provides a vital structure for the practice of addiction medicine.

The present time is a period of considerable change in diagnostic concepts and terminology. One of the principal diagnostic systems, the Diagnostic and Statistical Manual of Mental and Behavioural Disorders, has recently published its fifth edition (DSM-5) (American Psychiatric Association 2013). Substance use disorders have been radically restructured within it, and this will be described below. At the present time, the International Classification of Diseases, which is the international basis for disease, morbidity, and mortality coding, is undergoing revision, with the 11th revision (ICD-11) being scheduled for publication in 2015. Changes to the diagnostic criteria of addictive disorders are contemplated, but the essential diagnostic concepts may be similar to the current version ICD-10 (World Health Organization 1992). Many addiction specialists in North America and elsewhere adopt the diagnostic concepts and criteria developed by the American Society of Addiction Medicine and the International Society of Addiction Medicine. The conceptual understanding of substance disorders is rather different in these formulations and the diagnostic criteria have only passing resemblance to those employed in the DSM and ICD systems. A further contrast is provided by the emphasis in the fields of epidemiology and public health on quantification of substance use and not to define specific behavioral or psychophysiological disorders.

It will be apparent from the foregoing comments that a synthesis of diagnostic concepts in the current classification systems is not possible. In this chapter we shall present a history of common concepts of substance use disorders and then review the key diagnoses in the current international diagnostic systems. Before this we shall briefly review the range of addictive (dependence-inducing) and potentially harmful psychoactive substances and also the patterns of substance use that need to be captured by a diagnostic classification system.

11.2 Diagnoses

11.2.1 The Range of Addictive Substances

There are many thousands of naturally occurring and synthetic substances that have the capacity to induce addiction, and new ones are continually being synthesized.

Substances with addictive potential tend to have acute psychological effects which consumers find pleasant, at least initially and in the majority of cases. They tend to cause euphoria and, in many cases, a sense of relaxation. Certain substances are valued because they relieve pain or sickness and therefore are described as having a medicinal effect as opposed to a primary hedonic one. The pharmacokinetic properties of the substance influence its addictive potential, with the rapidity of absorption (and therefore action), ease of penetrating the blood/brain barrier, and duration of action influencing the likelihood of recurrent self-administration and therefore addiction. Addictive potential is also influenced by the mode of administration, with the smoking and intravenous injecting routes inducing more rapid addiction than oral ingestion. Addictive substances tend to have a biphasic action, whereby the hedonic effect is typically followed by negative symptoms consequent on declining blood and tissue levels of the substance. The neurobiological changes which occur in this phase could be regarded as "restorative," with the aim of returning neuronal systems to their normal functioning state.

The propensity of psychoactive substances to induce addiction therefore ranges considerably depending on the mode of administration, the substance's pharmacodynamic and pharmacokinetic properties, and also the social setting in which the substance is taken. Caffeine as occurs in coffee, tea, and certain soft drinks and once considered a minor stimulant at the lowest end of the addiction spectrum is listed in modern systems such as DSM-5 (American Psychiatric Association 2013). Certain other substances have psychoactive properties and are harmful, but are not or only rarely addictive. These include most of the hallucinogens, where the acute psychoactive effects (often of a psychedelic or psychotomimetic nature) commonly result in clinical presentations but where addiction/dependence is very uncommon. Other substances such as sugar and certain commercial soft drinks exist in a borderline area where addiction is described, but is not typical and is often rare. Substances in this last domain will not be further considered in the present chapter.

Many prescribed and proprietary ("over the counter") medications have addictive potential. Because of the commercial value of these medications, there is controversy as to whether they should be termed addictive substances as opposed to their inducing physiological dependence. In the medical community there is a divergence of opinion between those who would exclude medication use when it is being prescribed through a prescription or advised by a medical practitioner and those authorities who regard the occurrence of a desire for repeated administration of such medications and the occurrence of withdrawal symptoms to indicate that addictive processes are present in the individual.

11.2.2 Excessive Use and Repeated Use

Diagnoses are applied to the use of psychoactive substances to denote:

- An episode of excessive use, producing clinically significant effects – termed acute intoxication but which may in severe cases be termed poisoning.

- Repeated substance use which places the person at risk of harmful consequences – this is typically termed "hazardous" use, "risky" use, or "unhealthy" use.
- Repeated use which is causing physical, mental, or neurocognitive damage – termed "harmful use" in ICD-10.
- Repetitive substance use which has resulted in personal or social problems – termed "substance abuse" in DSM-IV.
- Repetitive substance use which has the features of a syndrome where there is an internal drive to continue and self-perpetuating use – termed "substance dependence" in DSM-IV and ICD-10.
- Repetitive substance use which is causing some form of addictive or harmful consequence – this is the new DSM-5 formulation of "substance use disorder."
- Substance-related problems or disabilities, which encompass the multiple physical disorders, mental health disorders, neurocognitive impairments, and social, personal, occupational, and legal problems.

In the diagnostic systems covered in this chapter, not all of these diagnostic entities are incorporated.

11.2.3 Mechanisms Underlying Repetitive Substance Use

There are numerous psychological and social influences which determine whether a substance with psychoactive properties is actually used, periodically or repeatedly, and may potentially lead to harmful consequences and addiction. An important determinant is the availability of a particular substance in a society, and this is in turn may be determined by whether it is of plant origin and requires particular climatic conditions or level of rainfall to grow. Other substances are chemically synthesized and require a corresponding level of knowledge and technical equipment to produce.

Psychological mechanisms are involved in substance use becoming repetitive use, and classical conditioning theory, operant conditioning theory, and social learning theory all contribute to our understanding of how this eventuates. The reader is referred to suitable reviews for further reference.

Neurobiological mechanisms come into play in particular when a pattern of repetitive substance use has developed and result in that repetitive use tending to become more stereotyped and self-perpetuating, being driven by internal cues rather than external circumstances. The essential result of the neurobiological mechanisms of addiction is the generation of an internal driving force, which is enduring and which promotes further substance use even in the absence of external cues and continues to do so even when circumstances are inappropriate for substance use and the person may actually be experiencing harm as a result of that use. The driving force of what is termed substance dependence or addiction results in substance use occupying a more and more central role in the person's life, with other interests, enjoyments, activities, and responsibilities being relegated to the periphery. Much has been learned about the neurobiological

processes, and it appears there are interlinked neurocircuits which are "re-set" in a person with addiction. These subserve reward, alertness (excitation), and salience on behavioral control.

In summary, in the early period of psychoactive substance use, that use is influenced strongly by external circumstances and also by the person's mood state. As repeated use continues and dependence develops, the repetitive use reflects more the internal neurobiological mechanisms that have developed. It is these mechanisms that result in repetitive substance use becoming more and more syndromal and to produce the clinical disorders we recognize as addiction.

11.2.4 Concepts of Substance Use Disorders

11.2.4.1 Personality Disorder

In the first edition of DSM, published in 1952, substance misuse was included in the personality disorders (American Psychiatric Association 1952). Drug addiction was not specifically defined, but there was a statement that it was usually symptomatic of a personality disorder. The second edition, published in 1968 (American Psychiatric Association 1968), had substance use disorders classified within the personality disorders. There were no specific definitions or criteria and little description of the conditions. The diagnosis of drug dependence required "evidence of habitual use or a clear sense of a need for the drug" (American Psychiatric Association 1968).

11.2.4.2 The Disease Concept

Many groups view substance use disorders as reflecting a disease process, which is biologically determined and results in the individual having an individualistic reaction to a psychoactive substance and a relatively predictable natural history. This conceptualization influenced and was subsequently embraced by the self-help movements, such as Alcoholic Anonymous. Jellinek developed the concept of the disease of alcoholism in the 1940s and 1950s (Jellinek 1960), although in his later work he increasingly recognized the role of environmental influences. During the 1960s and 1970s, the concept that substance misuse might represent a disease process was dismissed by most scientists and professionals. Likewise, the role of genetic predisposition was thought to be inconsequential, with the familial aggregation of substance misuse explained by cultural influences, role modelling, or malfunction within families.

11.2.4.3 Epidemiological and Sociological Formulations

A third tradition may be described as the epidemiological and sociological one. Put simply, substance misuse and problems arise fundamentally because of the overall level of use of that particular substance in society. In the 1950s Ledermann (1960) proposed a relationship between the level of alcohol consumption in a community and the prevalence of alcoholism. The level of use is, in turn, influenced by the availability of alcohol, its manufacture and distribution, its price (importantly), and

cultural traditions and sanctions. Inherent in these conceptualizations is that individual pathology is considered of secondary importance. The social constructionist school views substance use problems as disaggregated, with no special relationship among them. This school of thought was concerned about the stigma attributable to diagnostic labels and the potential of treatment as a form of social control (Room 1989).

11.2.4.4 Learned Behavior

The 1970s saw the rise of social-cognitive theory (Bandura 1977) as an influential paradigm to explain the development and resolution of alcohol and drug problems. This school of thought teaches that the (many) influences that determined behavior in general apply to the uptake of substance use and the development of disordered use. Positive consequences encourage repeated use, negative ones the opposite. Patterns of substance use behavior could become established in this way, but, equally, repetitive substance use could be "unlearned." This led to the development of a range of cognitive behavior therapies, some of which aimed at moderated or "controlled" substance use (Sobell and Sobell 1993).

11.2.4.5 Clinical Syndrome

The need for an understanding of substance misuse which spanned these various discipline-bound conceptualizations and terms was largely met by the formulation of the concept of a "substance dependence syndrome" originally proposed with regard to alcohol dependence by Edwards and Gross in 1976 (Edwards and Gross 1976). The basis of the dependence syndrome was a clinical description of key clinical features in a way that was essentially theoretical and was not based on any particular etiological understanding of the disorder, be it biological, behavioral, or sociological. Rather, certain experiences, behaviors, and symptoms related to repetitive alcohol use were identified as tending to cluster in time and to occur repeatedly. The advantage of a descriptive account of dependence is that it can accommodate etiological models, but not be beholden to them.

The concept of the dependence syndrome applies to many other psychoactive substances that have the potential for reinforcement of use, including benzodiazepines, illicit and prescribed opioids, cannabis, inhalants, psychostimulants such as cocaine and the amphetamines, nicotine, caffeine, and anabolic steroids (Feingold and Rounsaville 1995; Owen and Tyrer 1983; Saha et al. 2006; Teesson et al. 2002). It may also apply to repetitive behaviors that do not involve self-administration of a psychoactive substance. These include pathological gambling and compulsive shopping and exercise (Lejoyeux et al. 2000; Potenza 2006). "Disordered gambling" has now been added to DSM-5 (American Psychiatric Association 2013).

The dependence syndrome has been at the heart of the classification systems of psychoactive substance use disorders since the 1980s (Krabman and Saunders 1996; Saunders 2006). It is the principal substance use disorder in DSM-IV and ICD-10 (World Health Organization 1992) and in the more recent revisions of DSM, namely, DSM-IIIR and DSM-IV (American Psychiatric Association 1968, 1994, 2000). However, in the latest revision DSM-5 published in May 2013,

the dependence syndrome is subsumed under substance use disorder or alcohol use disorder (American Psychiatric Association 2013).

11.2.4.6 Neurobiological Disorder

Neurobiological mechanisms come into play particularly when a pattern of repeated use has become established. They induce a driving force to use the substance in preference to other human activities or interests and do so in continuing and seemingly compulsive way. They cause reinforcement and indeed self-perpetuation of psychoactive substance use. Increases in tolerance favor consumption of larger and larger doses of the substance. The three key neurobiological changes in dependence are:

(i) Activation and then inhibition of brain reward systems, particularly involving dopaminergic transmission and opioidergic transmission. These have the effect of re-setting the reward systems such that larger amounts of the substance are needed to produce the desired effect and natural rewards are not as reinforcing (Volkow et al. 2004).

(ii) Recruitment of brain stress systems, including those subserved by glutamate neurotransmission and corticotrophin releasing factor (CRF) (Room 1989) and suppression or uncoupling of antistress systems (Roy and Pandey 2002).

(iii) Impairment of inhibitory control pathways from the prefrontal cortex to the mesolimbic systems, resulting in impaired decision-making capacity (Yücel and Lubman 2007).

(iv) Re-setting of the salience circuitry arising from the cingulate gyrus of the frontal lobe and changing the importance of substance use relative to other interest, activities, and responsibilities.

A publication on the neuroscience of addiction by the World Health Organization summarizes the key developments in biomedical research over this period (World Health Organization 2004).

Investigations into possible genetic influences have accompanied this research on neural circuitry. Biometric genetic studies have shown that children born of parents with substance dependence are more likely to have substance dependence themselves (Saunders 1982) and that this is largely explained by genetic transmission rather than environmental factors (Ball 2008; Saunders 1982). Genomic analysis in human and laboratory animals has identified several areas of the genome where mutations are associated with increased risk of substance use disorders (Ball 2008).

11.2.5 Substance Use Diagnoses in DSM-IV, DSM-5, and ICD-10

Although many different systems of diagnosis and classification have been proposed for substance use disorders over the years, two have international recognition. They are the Diagnostic and Statistical Manual of Mental Disorders (DSM) of the American Psychiatric Association, Fourth and Fifth Editions (DSM-IV and DSM-5 respectively) (American Psychiatric Association 1994, 2000, 2013),

which covers only mental and behavioral disorders, and the International Classification of Diseases (ICD) of the World Health Organization (World Health Organization 1992), now in its Tenth Revision (ICD-10), which is a classification of all diseases, injuries, and causes of death.

11.2.6 Substance Dependence

Substance dependence is defined similarly in DSM-IV and ICD-10 (Table 11.1). The dependence syndrome is defined in DSM-IV and ICD-10 as a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated drinking or substance use and which tend to be self-perpetuating. Typically it occurs in people who use large amounts of psychoactive substances repeatedly consuming alcohol in excess of 120 g/day (men) or 80 g/day (women). The diagnosis of substance dependence is not, however, primarily made on the level of consumption but on criteria based largely on the original Edwards and Gross formulation (Edwards and Gross 1976). The criteria in the two systems (in summary format with comments) are listed in Table 11.1.

Substance dependence in DSM-IV is defined very similarly to ICD-10. As with all diagnostic systems, to be of optimal use in the clinic or for the needs of epidemiology and public health planning, the criteria must be both valid and straightforward, and this was foremost in the minds of those who fashioned them. The dependence syndrome applies to most psychoactive substances that have the potential for reinforcement of use (such as benzodiazepines, opioids, cannabis, psychostimulants, and nicotine). However, elements of the syndrome are not necessarily applicable to all substances, for example, hallucinogens. Dependence may also apply to repetitive behaviors that do not involve substance use such as gambling, compulsive shopping, and compulsive exercise (Lejoyeux et al. 2000; Potenza 2006).

Substance dependence does not feature in DSM-5. In its place is the broader and more disaggregated condition of "substance use disorder." This will be discussed further below. The criteria for substance-induced disorder are listed in Table 11.1 for the purpose of comparison with dependence.

11.2.7 Substance Withdrawal

The substance withdrawal syndrome refers to a state which may occur in persons with the dependence syndrome (ICD-10; DSM-IV) and (in a smaller proportion) with substance use disorder (DSM-5). The substance withdrawal syndrome refers to a state seen in persons with the dependence syndrome when use is curtailed. It is an important manifestation of the neurobiological changes that underpin dependence. In general the features of the withdrawal syndrome are opposite to those of the acute pharmacological effects of the substance. In contrast to dependence, the withdrawal syndrome varies appreciably according to the substance. Psychostimulant withdrawal is very different to withdrawal from sedative/hypnotics.

Table 11.1 Diagnostic criteria for dependence/alcohol use disorder/substance use disorder in ICD-10, DSM-IV, and DSM-5

	ICD-10 dependence	DSM-IV dependence	DSM-5 alcohol use disorder/substance use disorder
Stem		A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by 3 or more of the following occurring at anytime in the same 12-month period	A problematic pattern of alcohol (other substance) use leading to clinically significant impairment or distress, as manifested by at least two of the following occurring within a 12-month period
1. New in DSM-5	A strong desire or sense of compulsion to take the psychoactive substance *(craving or compulsion)*	No equivalent criterion – mentioned in text	Craving or a strong desire or urge to use alcohol (or other substance)
2.	No equivalent criterion but text states that the subjective awareness of compulsion is most commonly seen during attempts to stop or control substance use	There is persistent desire or unsuccessful attempts to cut down or control substance use	There is persistent desire or unsuccessful efforts to cut down or control alcohol (or other substance) use
3.	Difficulties in controlling substance-taking behavior in terms of its onset, termination, or levels of use *(loss of control)*	The substance is often taken in larger amounts or over a longer period of time than was intended	Alcohol (or other substance) is often taken in larger amounts or over a longer period than was intended
4.	Progressive neglect of alternative pleasures because of psychoactive substance use or increased amount of time necessary to obtain or take the substance or to recover from its effects	Important social, occupational, or recreational activities are given up or reduced because of drinking or psychoactive substance use	Recurrent alcohol (or other substance) use resulting in a failure to fulfil major role obligations at work, school, or home
5.	Subsumed in above criterion	A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects	A great deal of time is spent in activities necessary to obtain alcohol(or other substance), use alcohol (or other substance), or recover from its effects

(*continued*)

Table 11.1 (continued)

	ICD-10 dependence	DSM-IV dependence	DSM-5 alcohol use disorder/substance use disorder
6.	Tolerance: such that increased doses of the psychoactive substances are required in order to achieve effects originally produced by lower doses	Tolerance: as defined by either (a) a need for markedly increased amounts of the substance to achieve the desired effects or (b) markedly diminished effect with continued use of the same amount of the substance	Tolerance is defined by either of the following: (a) a need for markedly increased amounts of alcohol (or other substance) to achieve intoxication or desired effect or (b) a markedly diminished effect with continued use of the same amount of alcohol (or other substance)
7.	A physiological withdrawal state when substance use has ceased or been reduced, as evidenced by the characteristic withdrawal syndrome for the substance or use of the same (or a closely related substance) with the intention of relieving or avoiding withdrawal symptoms	Withdrawal as manifested by either (a) the characteristic withdrawal syndrome for the substance or (b) the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms	Withdrawal is manifested by either of the following: (a) the characteristic withdrawal syndrome for alcohol (or other substance) (b) Alcohol (or a closely related substance such as a benzodiazepine) (or other substance) is taken to relieve, or avoid withdrawal symptoms
8.	Persisting with substance use despite clear evidence of overtly harmful consequences	The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance	Continued alcohol (or other substance) use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol (or other substance)
9. Former DSM-IV abuse		Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g., arguments with spouse about consequences of intoxication, physical fights)	Alcohol (or other substance) use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol (or other substance)

(*continued*)

Table 11.1 (continued)

ICD-10 dependence	DSM-IV dependence	DSM-5 alcohol use disorder/substance use disorder
10. Former DSM-IV abuse	Recurrent substance use in situations in which it is typically hazardous (drink driving)	Recurrent use in situations in which it is physically hazardous
11. Former DSM-IV abuse	Recurrent substance use which results in failure to fulfil major obligations at work, school, or home	Important social, occupational, or recreational activities are given up or reduced because of alcohol (or other substance) use
Omitted	Recurrent substance-related legal problems (e.g., driving an automobile or operating a machine when impaired by substance use)	

In DSM-5 the diagnosis of alcohol (or substance) use disorder is further classified according to severity:
Presence of 2–3 symptoms, mild; presence of 4–5 symptoms, moderate; presence of 6 or more symptoms, severe

Substance withdrawal is often listed as a "substance-induced disorder"; however, given its intimate relationship with dependence, it is discussed at this point.

The withdrawal syndrome is defined in the international diagnostic systems as a group of symptoms of variable clustering and severity that occur on absolute or relative withdrawal of a substance after repeated, and usually prolonged and/or high dose, use of that substance. The specific criteria in ICD-10, DSM-IV, and DSM-5 are listed below in Table 11.2. The onset and course of the withdrawal state are time limited and are related to the type of substance and the dose being used immediately before abstinence. Three types of withdrawal are recognized in the ICD-10 and DSM-IV criteria: simple uncomplicated withdrawal, withdrawal with convulsions, and withdrawal with delirium (American Psychiatric Association 1994, 2000; World Health Organization 1992). Cannabis withdrawal was not recognized in DSM-IV, although it is now included in DSM-5 (American Psychiatric Association 2013).

11.2.8 Nondependent Repetitive Substance Use

Repetitive substance use which does not fulfill the criteria for the dependence syndrome is still of clinical significance. It is handled differently in the two systems. In ICD-10 the term harmful use applies to repetitive use of a psychoactive substance which has caused physical or mental harm to that person. In DSM-IV the

Table 11.2 Diagnostic criteria for substance withdrawal in ICD-10 and DSM-IV and for alcohol withdrawal in DSM-V

	ICD-10 substance withdrawal syndrome	DSM-IV (TR) substance withdrawal syndrome	DSM-5 alcohol withdrawal syndrome
1.	Clear evidence of recent cessation or reduction of substance use after repeated and usually prolonged and/or high dose use of that substance. One of the main indicators of the dependence syndrome	(A) The development of a substance-specific syndrome due to cessation of, or reduction in, substance use that has been heavy and prolonged	(A) Cessation of (or reduction in) alcohol use that has been heavy and prolonged
2.	Symptoms and signs compatible with the known features of a withdrawal state from the particular substance or substances. Physical symptoms vary according to the substance being used. Psychological disturbances (e.g., anxiety, depression, sleep disorders) are also common features of withdrawal. Typically the patient reports that withdrawal symptoms are relieved by further substance use	(B) The substance-specific syndrome causes clinically significant distress or impairment in social, occupation, or other important areas of functioning	(B) Two (or more) of the following developing within several hours to a few days after cessation of (or reduction in) alcohol use described in criterion A:
			1. Autonomic hyperactivity (e.g., sweating, PR $>$ 100 bpm)
			2. Increased hand tremor
			3. Insomnia
			4. Nausea or vomiting
			5. Transient visual, tactile, or auditory hallucinations or illusions
			6. Psychomotor agitation
			7. Anxiety
			8. Generalized tonic–clonic seizures
3.	The features are not accounted for by a medical disorder unrelated to the substance use and not better accounted for by another mental or behavioral disorder	(C) The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder	(C) The signs and symptoms in criterion B cause clinically significant distress or impairment in social, occupational, or in other important areas of functioning

term substance abuse refers to repetitive use of a psychoactive substance which essentially is causing social harm or problems. There is no equivalent term in ICD-10; indeed ICD-10 eschews the motion of a disorder that is defined by social criteria. Other nondependence conditions have been proposed and tentatively defined; they are covered later.

11.2.8.1 Substance Abuse

Substance abuse is defined in DSM-IV as repeated substance use that leads to one or more social or occupational problems. It is understood as a less severe condition than dependence. The two diagnoses cannot coexist in the same time period,

as substance abuse is preempted by a diagnosis of dependence. Substance abuse can be envisaged as one axis of a biaxial conceptualization of substance use disorders, which separates the core syndrome of dependence from the consequences. However, there is blurring of this conceptualization because of its hierarchical relationship with dependence, i.e., as a less severe disorder. The extent to which the biaxial relationship applies and indeed whether abuse is properly separated from dependence remains controversial, with some studies finding a one factor solution that covers the spectrum of abuse and dependence criteria being optimal (Edwards et al. 1981; Nelson et al. 1999; Teesson et al. 2002). DSM-5 does not have a separate diagnosis for substance abuse which is subsumed under substance use disorders.

11.2.8.2 ICD-10 Harmful Use

Harmful substance use is a repetitive pattern of substance use, at levels which result in actual physical or mental harm, but does not fulfill the criteria for the dependence syndrome. The harmful effects may be acute or chronic. Examples of acute complications include fractures and other forms of trauma, acute gastritis, and acute psychotic symptoms following substance use. Chronic medical complications encompass liver disease (e.g., alcoholic liver disease or hepatitis C-induced liver disease following injecting drug use), cardiovascular diseases, respiratory diseases, various neurological sequelae, and many others. Examples of mental complications are depressive episodes secondary to heavy alcohol intake and substance-induced psychosis. In clear distinction to DSM-IV, social complications per se are insufficient to justify a diagnosis of harmful use under the WHO nomenclature (Saunders 2006; World Health Organization 1992).

11.2.9 Broadening the Definition: Substance Use Disorder in DSM-5

As mentioned above, DSM-5 has radically restructured the conceptualization and classification of substance-related disorders (American Psychiatric Association 2013) (Table 11.1). Substance dependence and abuse have been replaced by the broader concept of substance use disorder.

11.2.9.1 Alcohol (Substance) Use Disorder

Alcohol (substance) use disorder is defined in DSM-5 as a cluster of cognitive, behavioral, and physiological symptoms (which can include withdrawal, tolerance, and craving), indicating that the individual continues using the substance despite significant substance-related problems. Substance use disorders are classified separately under 10 separate classes of drugs, viz., alcohol, caffeine, cannabis, hallucinogens, inhalants, opioids, sedatives/hypnotics/anxiolytics, stimulants, tobacco, and other (unknown) substances.

Alcohol use disorder is defined as a problematic pattern of alcohol use leading to clinically significant impairment or distress, as manifested by at least two of 11 criteria (Table 11.1) occurring within a 12-month period.

11.2.10 Other Definitions of Addiction or Dependence

The two systems that have most impact internationally are the ICD and the DSM, under the auspices of the World Health Organization and the American Psychiatric Association (APA) respectively. Several professional organizations have developed definitions for use by their own members/fellows (the APA is a national professional organization, but the DSM has such international reach that it is more appropriately classified as an international system). Foremost of these other organizations is the American Society of Addiction Medicine (ASAM). It employs the term addiction rather dependence or "use disorders." The ASAM definition of addiction (American Society of Addiction Medicine 2011) is as follows:

> Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviours.
>
> Addiction is characterized by inability to consistently abstain, impairment in behavioural control, craving, diminished recognition of significant problems with one's behaviours and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death.

This is a fundamentally different concept to those of dependence in the ICD and DSM systems and even more distant to the DSM-5 understanding of substance use disorders. The main points of distinction are:

1. The disorder is described as "primary" and suggests a fundamental (presumably) biological difference between those who are addicted and those who are not, rather than the notion of an acquired syndrome which is the nature of the dependence syndrome.
2. The disorder is described as "progressive" in an unqualified way, which is different to the concept that dependence can undergo "natural" remission (i.e., without treatment).
3. There is no sense of a spectrum of disorder.

There are five central features of addiction in this conceptualization, which are:

(a) Inability to consistently *a*bstain
(b) Impairment in *b*ehavioral control
(c) *C*raving, or increased "hunger" for drugs or rewarding experiences
(d) *D*iminished recognition of significant problems with one's behaviors and interpersonal relationships
(e) A dysfunctional *e*motional response

These features (note they are abbreviated ABCDE) might be considered diagnostic criteria for addiction, although it is not clear how many are required for the diagnosis and in what combination. The psychometric performance of the criteria is unknown. Despite these shortcomings, the ASAM definition well summarizes the experience of patients at the severe end of the spectrum of substance use disorders. It has an intuitive appeal to many clinicians, particularly those working in inpatient

treatment programs and residential recovery programs. The definition has been adopted, on a temporary basis, by the International Society of Addiction Medicine and the Canadian Society of Addiction Medicine.

11.2.11 Other Forms of Repetitive Substance Use

The disorders of substance dependence, substance abuse, harmful use, and (DSM-5) substance use disorder do not encompass the whole spectrum of damaging (or potentially damaging) substance use and pose limitations for prevention, for early intervention clinical work, and for epidemiological purposes. Several other conditions (or "states") were described in the report of a WHO Expert Committee, which was published in 1980 (Edwards et al. 1981). These were:

Unsanctioned use. This was defined as the use of a substance that is not approved by a society or by a group within that society. This term implies that this disapproval is accepted as a fact in its own right, without the need to determine or justify the basis of the disapproval.

Dysfunctional use. This is substance use that leads to impaired psychological or social functioning, for example, loss of employment or marital problems.

Hazardous use. This is repetitive substance use which places the person at risk of harmful consequences. In the WHO formulation, this was defined as physical and mental harm, but in other definitions harm has been taken to incorporate social and legal consequences too. Hazardous substance use is sometimes referred to as "at risk," "risky" or "medium," or "high risk" substance use.

Of these, only "hazardous use" has survived as a term in common use, and even so it does not feature in ICD-10. It, or similar terms, has been operationalized for alcohol consumption in several countries. For example, in the USA, men who drink five or more standard drinks (65 g alcohol) in a day or more than 15 standard drinks (195 g) per week and women who drink more than four standard drinks (50 g) in a day or eight standard drinks (105 g) per week are considered to be drinking excessively (National Institute on Alcohol Abuse and Alcoholism 2005; Saha et al. 2006). Repeatedly consuming 5+ (men) or 4+ (women) US standard drinks (65 and 50 g alcohol respectively) confers a risk of alcohol use disorders and acute and chronic illnesses and injuries (Dawson et al. 2005; Russell et al. 2004). In Australia hazardous or risky consumption has been defined for some years as repeated daily consumption of more than four Australian standard drinks (40 g alcohol) for a man and more than two standard drinks (20 g alcohol) for a woman (Dawson 2000), although in the most recent publication, the criteria for men have been reduced to the same level as for women. In some Asian countries hazardous or risky drinking indicates consumption at levels that lead to intoxication twice a month or more.

The application of hazardous or "risky" use to other substances has been slower. For nicotine (tobacco), it can be argued that there is no nonhazardous level of use. Likewise, because of uncertainties as to whether there is truly a safe or low-risk level of use for other substances, the concept has not been applied widely to illicit

drugs such as cannabis, the amphetamines, cocaine, or heroin, although research on quantifying and establishing the risk of low-level cannabis use is emerging. For epidemiological and public health purposes, having a term that defines various levels or patterns of substance use as conferring risk is advantageous. Indeed, recent data from the National Epidemiologic Survey of Alcohol and Related Conditions (NESARC) indicate that hazardous alcohol consumption (defined as the US 5+/4+ standard drink criterion) exists within the continuum of abuse and dependence criteria (Saha et al. 2007). As the frequency of this level of consumption increases, this experience moves along the severity continuum to overlap with abuse and dependence criteria (Saha et al. 2007).

At the same time, to examine relationships between use patterns and consequences without considering whether a diagnosable substance use disorder is present, as is usual in epidemiological studies, is limiting. The reduction in all-causes mortality among people with moderate levels of alcohol consumption is not seen in those who have had a previous diagnosis of alcohol dependence (Dawson 2000). In support of including hazardous use in a diagnostic system is the evidence that it can be defined and it responds to therapy, the evidence base for the effectiveness of interventions for hazardous alcohol consumption being particularly strong (Bertholet et al. 2005; Kaner et al. 2009). Thus, in a comprehensive diagnostic system, there are grounds for having a dependence category, a nondependence disorder that is of clinical consequence and a "subthreshold" disorder that indicates risk to individuals and populations.

11.2.11.1 Diagnostic Orphans

A term that developed after DSM-IV was published was "diagnostic orphans." These are substance users who report some symptoms of dependence, but do not meet diagnostic criteria for either DSM-IV dependence or substance abuse. In young people it is a common category, as common (with respect to alcohol) as dependence or abuse (Eng et al. 2003). Alcohol diagnostic orphans have a natural history that is closest to that of alcohol abuse, though have fewer alcohol-related problems over time. Cannabis diagnostic orphans are also similar in use patterns to those with cannabis abuse (Degenhardt 2002). The term "diagnostic orphan" is now redundant given that DSM-5 has reduced the cutoff point for criteria for substance use disorder to two.

11.2.12 Substance-Induced Disorders

Substance-related problems (or disabilities) were conceptualized by the WHO Committee as the *consequences* of repetitive substance use (Edwards et al. 1981; Saunders 2006). They include both acute (short-term) effects and chronic (long-term) ones (Latt et al. 2009). Acute intoxication is usually placed within the substance-induced disorders, although it is a manifestation of the acute pharmacological effects of the substance. Its central features are listed in Table 11.3 (which provides the DSM-5 criteria).

Table 11.3 Diagnostic criteria for alcohol intoxication – DSM-V

(A) Recent ingestion of alcohol
(B) Clinically significant problematic behavior or psychological changes that developed during or shortly after alcohol ingestion
(C) One, or more, of the following signs or symptoms developing during or shortly after alcohol use:
(a) Slurred speech
(b) Incoordination
(c) Unsteady gait
(d) Nystagmus
(e) Impairment of attention or memory
(f) Stupor or coma
(D) The signs and symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication with another substance

In the remaining part of this chapter, we shall describe the common substance-induced mental disorders, with a brief comment only on substance-induced physical disorders.

11.2.12.1 Substance-Induced Mental and Neurocognitive Disorders

In DSM-IV and ICD-10 there are several substance-related mental disorders. These include substance-induced depression, substance-induced anxiety disorder, substance-induced bipolar disorder, and substance-induced psychotic disorder. In DSM-5 the same disorders are present, but they are located in the chapters describing the respective generic mental disorder. For example, substance-induced anxiety disorder is grouped within the Anxiety Disorders Section. A generic description of substance-induced mental disorders as per DSM-5 is provided as Table 11.4.

In addition, there are neurocognitive consequences of substance use disorders. Here we shall briefly describe one of the former, psychotic disorder, and two of the latter, delirium and amnesic syndrome.

11.2.12.2 Psychotic Disorder

Psychosis and/or psychotic symptoms occur in many people with substance use disorders. In some this reflects an underlying independent disorder such as schizophrenia. In others the psychosis is a consequence of drug use. In others the precise mechanism remains unclear. ICD-10 defines substance-induced psychotic disorder as a phenomenon that occurs during or immediately after psychoactive substance use (usually within 48 h) and is characterized by vivid hallucinations (typically auditory but often in more than one sensory modality), misidentifications, delusions and/or ideas of reference (often of a paranoid or persecutory nature), psychomotor disturbances (excitement or stupor), and an abnormal affect, which may range from intense fear to ecstasy (World Health Organization 1992). The sensorium is usually clear, but some degree of clouding of consciousness, though not severe confusion, may be present. The disorder typically resolves at least partially within one month

Table 11.4 Substance/medication-induced mental disorders – DSM-V

(A) The disorder represents a clinically significant symptomatic presentation of a relevant mental disorder
(B) There is evidence from medical history, physical examination, or laboratory findings of both of the following:
(a) The disorder developed during or within 1 month of substance intoxication or withdrawal or taking a medication
(b) The involved substance/medication is capable of producing a mental disorder
(C) The disorder is not better explained by an independent mental disorder, i.e., one that is not substance or medication induced. Such evidence of an independent mental disorder could include the following:
(a) The disorder preceded the onset of severe intoxication withdrawal or exposure to the medication
(b) The full mental disorder persisted for a substantial period of time (e.g., at least 1 month) after cessation of acute withdrawal or severe intoxication or taking the medication. This criterion does not apply to substance-induced neurocognitive disorders or hallucinogen persisting perception disorder, which persists beyond the cessation of acute intoxication or withdrawal
(D) The disorder does not occur exclusively during the course of a delirium
(E) The disorder causes clinically significant distress or impairment in social, occupational, or other important areas of functioning

and fully within six months. The diagnosis is excluded if the psychotic state is a manifestation of substance withdrawal syndrome. According to DSM-IV, a substance-induced psychotic disorder is defined by (i) prominent hallucinations or delusions developing during, or within a month of, substance intoxication or withdrawal, (ii) the phenomenon is etiologically related to the disturbance, and (iii) that the disturbance is not accounted for by a psychotic disorder that is not substance-induced (American Psychiatric Association 2000).

In DSM-5 (Table 11.5) substance/medication-induced psychotic disorders, is mentioned in the Chapter on Schizophrenia Spectrum and Other Psychotic Disorders with the psychotic disorder associated with alcohol, cannabis, phencyclidine, other hallucinogens, inhalants, sedative/hypnotic/anxiolytic, amphetamine (or other stimulant), cocaine, and other unknown substance. The psychotic symptoms are thought to be a physiological consequence of a drug of abuse (medication or toxin) and cease after removal of the agent. The onset of psychotic disorder during intoxication of a substance is differentiated from that with onset during withdrawal of the substance.

For psychostimulants such as amphetamines and cocaine, there is a dose–response relationship, with psychosis occurring especially in those who have been using high doses and/or over a lengthy period. According to ICD-10, a diagnosis of psychotic disorder should not be made merely on the basis of perceptual distortions or hallucinatory experiences when substances having primary hallucinogenic effects (e.g., lysergic acid (LSD), mescaline, and cannabis in high doses) have been taken. In such cases, and also for confusional states, a possible diagnosis of acute intoxication should be considered. DSM-IV has no such exclusion.

Table 11.5 Diagnostic criteria for substance/medication-induced psychotic disorder – DSM-V

(A) Presence of one or both of the following symptoms:
(a) Delusions
(b) Hallucinations
(B) There is evidence from the history, physical examination, or laboratory findings of both (a) and (b):
(a) The symptoms developed during or soon after substance intoxication or withdrawal or after exposure to a medication
(b) The involved substance/medication is capable of producing the symptoms in criterion A
(C) The disturbance is not better explained by a psychotic disorder that is not substance/medication induced. Such evidence of an independent psychotic disorder could include the following: The symptoms preceded the onset of the substance/medication use; the symptoms persisted for a substantial period of time (1 month) after the cessation of acute withdrawal or severe intoxication; or there is evidence of an independent non-substance/medication-induced psychotic disorder (e.g., history of recurrent non-substance/medication-related episodes)
(D) The disturbance does not occur exclusively during the course of a delirium
(E) The disturbance causes clinically significant distress or impairment of social, occupational, or other areas of functioning The diagnosis should be made instead of a diagnosis of substance intoxication or withdrawal only when symptoms in Criterion A predominate in the clinical picture and when they are sufficiently severe to warrant clinical attention

11.2.12.3 Delirium

Delirium is an uncommon feature of substance misuse, although sometimes the diagnosis is made in persons with acute intoxication. Substance intoxication with delirium is an accepted diagnosis in DSM (American Psychiatric Association 1994, 2000, 2013), but not in ICD-10 (World Health Organization 1992). Most commonly it is seen in those with a severe withdrawal syndrome from alcohol or sedative/hypnotic drugs. The classical disorder is delirium tremens (DTs) (Saunders and Janca 2000), which is a short-lived but occasionally life-threatening toxic-confusional state with accompanying somatic disturbances. It is usually a consequence of absolute or relative cessation of alcohol in severely dependent drinkers with a long history of use. Its onset may be preceded by features of simple withdrawal and/or by withdrawal convulsions. A similar withdrawal delirium is seen after cessation of benzodiazepines and other sedative/hypnotics although with less tremor. In DSM-5 substance intoxication delirium is differentiated from substance withdrawal delirium in the Chapter on Neurocognitive Disorders (American Psychiatric Association 2013).

11.2.12.4 Amnesic Syndrome

Amnesic (or amnestic) syndrome is an example of a substance-related disorder where, typically, neuronal loss has occurred (Table 11.6). The most common form is characterized by impairment of recent memory with relative preservation of remote memory and with normal immediate recall (American Psychiatric Association 1994, 2000; World Health Organization 1992). Disturbances of time sense and ordering of

Table 11.6 Diagnostic criteria for the amnesic syndrome/amnestic disorder

ICD-10 amnesic syndrome (World Health Organization 1992)	DSM-IV criteria for amnestic disorder (American Psychiatric Association 2000)
1. Memory impairment as shown in impairment of recent memory and learning of new material, disturbance of time sense (e.g., rearrangement of chronological sequence, telescoping of repeated events into one, etc.)	(A) The development of memory impairment as manifested by impairment in ability to learn new information or the inability to recall previously learned information
2. Absence of defect in immediate recall, impairment of consciousness, and generalized cognitive impairment	(B) The memory disturbance causes significant impairment in social or occupational functioning and represents a significant decline from a previous level of functioning
3. History of objective evidence of chronic (and particularly high dose) use of alcohol or drugs	(C) The memory disturbance does not occur exclusively during the course of a delirium or dementia and persists beyond the usual duration of substance intoxication or withdrawal
Includes Korsakov's psychosis or syndrome, alcohol or other psychoactive substance induced	(D) There is evidence from history, physical examination, or laboratory finding that the memory disturbance is etiologically related to the persisting effects of substance use

events are usually evident, as are difficulties in learning new material. Confabulation may be marked, but is not invariably present and should not be regarded as a prerequisite for diagnosis. Importantly, other cognitive functions are usually relatively well preserved; the amnesic defects are therefore out of proportion to other disturbances. Personality changes, often with apparent apathy and loss of initiative, and tendency towards self-neglect may be present, but is not regarded as necessary for diagnosis. The amnesic syndrome is not specified as such in DSM-5, but is listed under substance/medication-induced major or mild neurocognitive disorder.

11.2.12.5 Substance-Related Physical Disorders

Alcohol consumption can affect virtually every organ system in the body, while cannabis and tobacco commonly induce respiratory complications. Repetitive psychostimulant use can lead to a range of psychiatric syndromes, including mood disorder and psychotic disorder. Complications arising from repetitive substance use stem not only from the pharmacological properties of a particular substance but from unknown potency, purity, and sterility from contaminants and adulterants with which the substance is prepared, unsafe injecting practices, and the associated lifestyle of the user. The spread of bacterial infections and viral infections, such as hepatitis C and HIV, and to a lesser extent hepatitis B, is important in this regard (American Society of Addiction Medicine 2011; Latt et al. 2009). The disinhibiting effect of alcohol and substance use also places users at risk of sexually transmitted diseases.

In DSM-III, DSM-IIIR, and DSM-IV, relevant physical disorders were noted in Axis III of the multiaxial system. DSM-5 has abandoned this multiaxial system and

comorbid physical disorders receive little attention. ICD-10 by contrast lists an array of these disorders, in keeping with its objective of encompassing all human disorders irrespective of etiology.

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Screening, Early Detection and Brief Intervention for Alcohol Use Disorders

12

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Contents

Abstract

Self-recognition of an alcohol use disorder is often late in the natural history of this condition. Because of this and the limited impact of treatment for patients with late-stage complications of their alcohol problem, there has been considerable effort made to identify alcohol consumption where it has reached a hazardous or risky stage or is starting to cause problems, before dependence becomes

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entrenched and complications irreversible. The approach of screening and brief intervention represents a secondary intervention approach, which aims to help people reduce their alcohol consumption to low risk levels, and thereby avoid progression to dependence and the development of physical and mental sequelae and social problems. This chapter describes the development of screening instruments such as the Alcohol Use Disorders Identification Test (AUDIT) and several derivatives and alternatives. The performance and applicability of the screening instrument is reviewed. Following this there is an account of brief intervention approaches which aim to provide succinct information on alcohol use and risks to the individual, often combined with brief motivational and behavioral strategies. There is considerable evidence from scores of randomized controlled trials and meta-analyses for the effectiveness of brief interventions in reducing hazardous alcohol consumption and alcohol-related problems. In the long term follow-up studies there is also evidence for reduced rates of hospitalization and mortality rates. The latest developments in screening and brief intervention are their presentation in various electronic formats. Online screening with feedback and brief intervention has shown to be efficacious and has the potential to be accessible to a greater section of the general population than face-to-face interventions in health care settings.

12.1 Introduction

12.1.1 Broadening the Spectrum of Intervention for Alcohol Use Disorders

Self-recognition of an alcohol use disorder is often late in the natural history of the condition. Frequently, patients seen in healthcare services have well-established alcohol dependence and often physical, neurocognitive, and psychiatric complications when they present for treatment. At this stage, the road back to reasonable health and well-being is a long and sometimes uncertain one, requiring considerable personal resources, involvement in treatment, support, and lifestyle changes.

An important movement in the recent years has been to broaden the spectrum of responses so that people with hazardous (or unhealthy) alcohol consumption and those with less severe alcohol use disorders, as well as those with alcohol dependence, have an opportunity to be alerted to the risks of their drinking and to change their consumption patterns in a healthy direction. Screening and brief intervention has its origins in the work of a WHO Expert Committee in the late 1970s. In its report, the Expert Committee recommended "the development of methods for identifying and modifying potentially harmful patterns of alcohol consumption before dependence developed and disease was entrenched".

Arising from this report was a WHO program of work by on development of techniques for early detection and intervention for hazardous and harmful alcohol consumption. Parallel work in the area was undertaken by pioneers such as

Kristenson et al. (1983) and Heather et al. (1987). Since those early days, there has been a substantial effort to develop screening instruments, such as the Alcohol Use Disorders Identification Test (AUDIT) and the development of brief structured therapies designed to be used at the time hazardous and harmful alcohol use is identified.

This approach has been endorsed by many authorities. In 1990, an influential report from the US Institute of Medicine recommended that healthcare responses should extend beyond the provision of treatment for people with established alcohol dependence (or "alcoholism") to encompass early detection and treatments in primary care and in other non-specialist settings. It noted the evidence accumulating for the effectiveness of opportunistic screening and brief intervention for hazardous and harmful alcohol consumption. In the United Kingdom, the National Institute for Health and Clinical excellence in 2010 supported the widespread implementation of brief intervention approaches.

Screening and brief intervention is analogous to screening for asymptomatic hypertension and hyperlipidemia and indeed screening for a range of medical, mental, and social disorders. It is predicated on the basis that early detection and treatment of a disorder in its developmental stage has advantages over treatment of the established disorder in terms of reduced morbidity, better and more guaranteed response to treatment, and the avoidance of the costs of treating the advanced disorder and prevention of premature mortality.

This chapter will (1) review the current criteria for hazardous/unhealthy alcohol consumption, (2) examine the available screening instruments (focusing on instruments specifically derived to screen for a range of hazardous consumption and alcohol use disorders), (3) review the evidence for the effectiveness of brief interventions, (4) examine the implementations of such interventions in healthcare systems, and (5) conclude with an outline of the key therapeutic components of brief interventions. Mention will also be made of electronic screening and brief intervention which has been developed to further broaden the access of people with hazardous or unhealthy patterns of alcohol consumption to information and advice, who otherwise might not be engaged in the healthcare system.

12.2 Screening and Brief Interventions

12.2.1 The Spectrum of Hazardous Consumption and Alcohol Use Disorders

Alcohol use and misuse exist as a continuum, and an important realization is that harm can occur at many points along this continuum. Accidents can occur due to a single episode of excessive consumption, and they are more likely to occur with repeated bouts of drinking; social problems can arise due to intoxicated behaviors, and acute medical disorders may also arise from periodic binges. Many chronic disease states are linked to regular consumption of alcohol that may not reflect alcohol dependence. Although the risks of all these are multiplied on people who

have alcohol dependence, and it is right that much attention be paid to this group, it is important to capture a broad range of consumption patterns and alcohol disorders.

The risk of harm is related to the level of alcohol consumption and the frequency and duration of consumption. For many harmful consequences, there appears to be a threshold of consumption below which harm is not seen or occurs only infrequently. In many countries, national authorities have defined hazardous (or risky or unhealthy) alcohol use. Some examples are as follows:

(a) *United States*: for women, more than seven drinks per week or more than three drinks per occasion and, for men, more than 14 drinks per week or more than four drinks per occasion (one drink being approximately 13 g of alcohol) (US Preventive Services Task Force 2013).
(b) *United Kingdom*: for men, over 40 g alcohol (five units) per day or 21 units per week and, for women, over 24 g alcohol (three units) per day or 14 units per week (one unit approximately equivalent to 8 g alcohol) (SIGN Guidelines 2003).
(c) *Australia*: more than two standard drinks on any day (for both men and women) or more than four standard drinks on a single occasion (one standard drink being approximately 10 g of alcohol). For those under the age of 16 years or if a woman is pregnant or planning to become pregnant or breastfeeding, the safest option is not to drink alcohol (NH & MRC 2009).

The term alcohol use disorders is typically used to denote a repetitive pattern of alcohol consumption. It may be facilitated by external factors such as cultural norms and practices, peer pressure, work culture, and work pressure or internal factors such as the person's feelings and mental state or desire to experience the euphoria and state of intoxication that alcohol can cause. Non-dependent alcohol use disorders include ICD 10 harmful alcohol use, DSM-IV alcohol abuse, and part of the spectrum of the recently defined DSM-V alcohol use disorder. DSM-IV alcohol abuse is defined as a maladaptive pattern of alcohol use over a twelve-month period, leading to clinically significant failure to fulfill major obligations at work, school, or home; legal problems; or interpersonal problems, or when it is physically hazardous. "Unhealthy alcohol use" is a term referring to that spectrum of alcohol use that can result in health consequences and broadly covers hazardous/harmful drinking, alcohol abuse, or alcohol dependence (Saitz 2005; Saitz et al. 2013).

Alcohol dependence is a psychobiological syndrome and is best understood as a disorder where there is a persistent internal drive to consume alcohol such that alcohol increasing takes "center stage" in the person's life and other enjoyments, activities and responsibilities are pushed to the periphery. It reflects enduring changes in key neurocircuits that subserve reward, alertness, response control, and salience in the ventral tegmental area of the midbrain, the nucleus accumbens, and related structures of the lower forebrain and with projections to and from the prefrontal gyrus and the circulate gyrus of the cortex. It is more "disease-like" than any other form of repetitive alcohol use and tends to be self-perpetuating and to run true when active at different periods in the person's life.

For this spectrum of hazardous alcohol use and alcohol use disorder, there is a need for reliable methods of screening and intervention. The term "screening and

brief intervention" is typically directed at hazardous use and nondependent alcohol use disorders. However, screening and early detection can be applied to alcohol dependence, and brief interventions can be adapted and can be used in therapy at the start of treatment for persons with alcohol dependence.

12.2.2 Development of the AUDIT and Other Screening Instruments

The modern era of screening for hazardous alcohol consumption and alcohol use disorders began with the development of the Alcohol Use Disorders Identification Test (AUDIT) (Saunders and Aasland 1987; Saunders et al. 1993; Babor et al. 1992). Prior to the development of the AUDIT, alcohol screening instruments focused on the detection of alcoholism. They were not designed to detect the range of alcohol use disorders or hazardous/unhealthy alcohol consumption, the reason being that these concepts had not gained general acceptance at the time the older instruments were introduced. These older instruments include the Michigan Alcoholism Screening Test (MAST), developed in 1971 and which exists in several versions including brief ones and the four-item CAGE (Ewing 1984).

The AUDIT has its origins in the WHO collaborative work that was initiated by the Expert Committee and was derived from findings in a World Health Organization collaborative study. The AUDIT was developed from the empirical selection of items contained in a WHO assessment instrument, comprising more than 150 questions. Participating centers from six countries around the world (which represented different cultures, healthcare systems, stages of economic development and political systems) were involved. The ten items which formed the AUDIT were those which had the following characteristics:

1. They had the highest or comparably high item-to-total correlations with the domains they represented.
2. Individually and collectively they had the greatest discriminatory value between patients who had hazardous consumption and/or alcohol use disorders and those who did not.
3. The questions not only conformed to the then bi-dimensional concept of alcohol dependence and its consequences but extended it to a tridimensional concept of (i) intake measures, (ii) measures of the urge or drive to consume alcohol (and putative dependence), and (iii) direct or proxy measures of alcohol-related consequences.
4. The sensitivity and specificity and positive and negative predictive values for the AUDIT in clinical and also epidemiology populations indicated a high degree of accuracy of classification and therefore practical utility.
5. Likewise the sensitivity and specificity of questions in the three individual domains were psychometrically acceptable.
6. The questionnaire as a whole and questions within the three domains had acceptable psychometric performance as judged by measures such as Cronbach's Alpha Coefficient.

7. Each individual question had high face validity and the meaning of the question was clear and it explicitly mentioned the link with alcohol consumption.
8. Each question was suitable in providing a means of exploring further the patient's experiences with alcohol and the questionnaire as a whole was suitable as a framework for intervention.
9. The individual questions could be translated readily and accurately (both grammatically and idiomatically) into major world languages.

Subsequent studies showed that the AUDIT Questions:

1. Performed as a stand-alone questionnaire as it did when the questions were embedded in a general health screening instrument
2. Had high acceptance among populations being screened
3. Could be adapted easily to electronic format including interactive media where feedback on the AUDIT score and on responses to individual questions could be provided

The AUDIT questionnaire offers a simple and systematic way of assessing alcohol intake (Questions 1–3), alcohol dependence (Questions 4–6), and alcohol-related harm (Questions 7–10). The questionnaire may be self-administered while the patient is awaiting the consultation or may be used by the clinician during the assessment. Responses in the AUDIT are quantified from 0 (far left column) to 4 (far right column) for Questions 1–8 and 0, 2, and 4 for Questions 9–10. The AUDIT score may range from 0 (for an abstainer of alcohol) to 40. A presumptive diagnosis of hazardous or harmful consumption is made if the AUDIT score is 8 or above. More severe harm and dependence are likely when the score is 13 or more and to be extremely likely if the score is 20 or more. The scores on the AUDIT can also point to the intervention required, if any. Scores of 0 and 1–7 may result in some feedback but otherwise no specific intervention. A score of 8 or more merits a brief intervention, with scores of 13 or more (and certainly 20 or more) alerting the clinician to the need for detoxification and referral for specialist treatment. Assessment by completion of the AUDIT questionnaire itself is reported to reduce hazardous drinking (Kypri et al. 2007)

Several derivatives of the AUDIT have been published over the years. The most popular of these is the AUDIT-C, which comprises simply the first three questions of consumption measures. The shorter three-item AUDIT-C has been shown to be a more convenient and effective instrument for diagnosing alcohol use disorders in a primary care setting, viz.:

1. How often do you have a drink containing alcohol?
2. How many standard drinks containing alcohol do you have on a typical drinking day?
3. How often do you have four drinks (for women) and six drinks (for men) or more on one occasion?

Scores of 3 or more in women and 4 or more in men have a sensitivity of 73 % and 86 % and a specificity of 91 % and 89 %, respectively. (Bradley et al. 2007) A score of 7–10 or more indicates alcohol dependence (Rubinsky et al. 2010).

At a minimum, one question on the quantity of alcohol consumed can be asked. "How many times in the past year have you had five (for men) or four (for women) or more drinks in a day?" (a positive test was considered to be a response >0) was

found to be useful in primary care (Smith et al. 2009). In the FAST, the consumption question is "How often do you have eight (or for women six) or more standard drinks on one occasion?" A response of monthly or more is considered a positive answer. Three further questions make up the FAST (Hodgson et al. 2002) with a score of three or more indicating hazardous alcohol drinking.

Some alcohol screening instruments have been developed to identify hazardous consumption and alcohol use disorders within specific populations such as women, pregnant women, adolescents, and the elderly. These include the TWEAK to screen for alcohol use during pregnancy (Russell et al. 1991).

Another relevant screening test is the WHO Alcohol, Smoking and Substance Involvement Screening Test (ASSIST). ASSIST is a combined screen for drug and alcohol misuse and is available for self-completion while the patient is in the waiting room or hospital clinic. It is designed to inquire about alcohol use in context of health inquiries to detect problem or risky alcohol and other substance use in primary health care. It is linked to a brief intervention based on the acronym FRAMES and incorporates motivational interviewing (WHO ASSIST Working Group 2002; Newcombe et al. 2005).

In 2001, a smoking, nutrition, alcohol, and physical activity (SNAP) framework developed by the Australian government Department of Health and Aging (SNAP 2001) was found to fit well with general practice consultations (Harris et al. 2005).

12.2.3 Brief Interventions: Background and Evidence

Once a person has been identified, through screening or clinical inquiry, as having an alcohol use disorder, a brief, focused form of therapy is beneficial. The usual term to describe this is "brief alcohol intervention." As described above, brief intervention aims to engage with people who have hazardous or harmful alcohol consumption, using the DSM terms alcohol abuse (DSM-IV) or alcohol use disorder (DSM-V). The focused advice and therapy is provided before the person has developed alcohol dependence or severe physical, mental, or personal problems.

Brief intervention is therefore a proactive strategy comprising provision of brief advice on the consequences of hazardous/harmful drinking or alcohol abuse, feedback of harm and relating this to the patient's excess drinking, setting goals for safe levels of drinking, outlining benefits obtained from cutting down drinking, and setting strategies to overcome "at-risk" times. The intervention may take only 4–5 mins.

There is a wealth of evidence attesting to the effectiveness of brief alcohol interventions in reducing alcohol intake and alcohol-related problems in persons with alcohol use disorders. Approximately 50 randomized controlled trials of various forms of brief intervention compared with no intervention or an alternative form of intervention have been published. Furthermore, several meta-analyses have been published since the early 2000s. A Cochrane Collaboration review of 23 trials of a number of interventions, most commonly brief interventions, for preventing

injuries in problem drinkers reported 27–65 % reductions in alcohol or drinking-related injuries. However, in this analysis, there was insufficient evidence of reduced alcohol consumption (Dinh-Zarr et al. 2009). In other meta-analyses, Kaner and colleagues showed reduced alcohol consumption in men (although not in women). Longer counseling and extended treatments were found to have little additional effect over brief intervention (Kaner et al. 2007, 2009; Moyer et al. 2002).

The Cochrane Database of Systematic Reviews found that interventions for problem drinking, mainly brief counseling in the clinical setting, reduced injury-related deaths (relative risk (RR), 0.65; 95 % confidence interval (CI), 0.21–2.00), which may however have been due to chance. Brief counseling also showed beneficial effects on non-fatal injury outcomes such as falls, motor vehicle crashes, and suicide attempts. The authors felt that further studies are warranted (Dinh-Zarr et al. 2009).

The overall reduction in alcohol consumption between those receiving brief intervention and control groups receiving no advice or standard care is modest and amounts to approximately 10 g of alcohol per day. There are a greater effect on hazardous drinking and an even greater effect on alcohol-related injuries, with a relative risk of 0.68 (95 % CI 0.57–0.81) for hazardous alcohol consumption at 1 year (Kaner et al. 2007a, b) and 0.59 (95 % CI 0.42–0.84) for alcohol-related injury (Havard et al. 2008).

Furthermore, systematic reviews have shown that brief intervention reduces mortality over a 10-year follow-up, with a relative risk of 0.47 (95 % CI 0.25–0.89) (Wutzke et al. 2002; Cuijpers et al. 2004). The number needed to treat (NNT) is 58.8 to achieve mortality reduction. In relation to differential response according to experience of harm, brief interventions seem to be more effective in those people who are likely to experience problems related to alcohol than other alcohol consumers.

More recently, in a UK multicenter SIPS (Screening and Intervention Programme for Sensible drinking) trial, 3,562 primary care patients were screened for hazardous/harmful drinking using either the FAST or a single alcohol screening questionnaire. Patients randomized to three interventions were compared, each of which built on the previous one, namely, (i) a patient information leaflet control group, (ii) 5 mins of structured brief advice, and (iii) 20 mins of brief lifestyle counseling linked to motivational interviewing. The WHO screening instrument AUDIT (score of <8) was used as a primary outcome measure at 6 months. There was no difference in benefit between the three arms although patients in the 20-min intervention reported slightly greater satisfaction with treatment. The authors concluded that screening followed by simple feedback and written information may be the most appropriate strategy to reduce hazardous and harmful drinking in a primary care setting (Kaner et al. 2013).

The efficiency of screening and brief intervention will vary according to the prevalence of hazardous alcohol consumption in general practice when 10–15 % of patients in many Western countries would likely be hazardous drinkers; approximately eight people will need to be screened for each hazardous drinker to be

identified. Combining that with the NNT of 5–6 for alcohol consumption leads to the result that on average 45 patients in primary care will need to be screened for each person with hazardous alcohol consumption to become a low-risk drinker. This indicates the degree of effort required to provide brief intervention in practice although information on alcohol consumption is relevant to much of the health care when other issues such as the potential for interactions with medications and advice needed for pregnant women and people with a range of chronic medical disorders are taken into consideration.

12.2.4 Implementation of Screening and Brief Intervention in Clinical Practice

There is a wealth of evidence that demonstrates that brief interventions reduce hazardous and harmful alcohol consumption, as judged by overall alcohol consumption, reduced frequency of binge drinking, alcohol-related problems, and various secondary measures such as healthcare utilization. Some of the findings vary from study to study and among the meta-analyses. However, the overall message is clear that for these interventions, benefits are clear and the strength of the evidence would suggest that their general availability in the healthcare system should be assured. The reality is somewhat different.

Brief interventions are some of the most consistently effective and potent interventions directed at individuals and considerable effort is being made to incorporate them into the healthcare system. This is proven to be more difficult than originally anticipated. Very often, screening and brief intervention can be established as a brief project, but it tends not to be continued in any systematic way when external support and interest cease.

It is fair to say that screening and brief intervention has not been taken up in the healthcare system as avidly as had been expected. Certainly systematic screening in primary care and the delivery when appropriate of a brief therapy remain unusual, even in healthcare systems that have a strong primary prevention and population health orientation. Various barriers to implementation have been reported by health professionals and include (i) reluctance to inquire about alcohol consumption, (ii) poor role adequacy, (iii) inadequate resources to address alcohol use and problems, and (iv) poor role support (Nilsen 2010). There remains significant issues regarding training and confidence in providing brief interventions, issues of remuneration and competition for the time of medical practitioners and other health professionals given their overall responsibilities. Ethical considerations have also been raised as to the appropriateness of introducing a health issue which is not on the patient's agenda when they booked the consultation. More broadly, there is debate about which healthcare professionals have the capacity to provide these interventions.

Detection and diagnosis of alcohol use disorders remains low, and it is estimated that of the 15–30 % of patients in primary care or hospital settings who have an alcohol use disorder, in only one-third of the cases is that disorder diagnosed.

Screening and early detection therefore has a greater role than leading to a brief intervention. Early detection can often result in the correct diagnosis being expedited, with the patient being spared unnecessary investigations. Equally important, knowledge of the alcohol use disorder may prevent months or indeed years of inappropriate or ineffective treatment for patients who have disorders that may be related to alcohol consumption, such as hypertension, esophagitis and gastritis, anxiety, depression, and recurrent headache. It can also often provide an answer for patients who have multiple nonspecific and seemingly unconnected symptoms.

Efforts to facilitate the implementation of screening and brief intervention in primary care began with the original WHO collaborative study. When evidence became available for the effectiveness of brief alcohol interventions in this collaborative study, thoughts were directed to how these interventions could be implemented in the primary care system. Phase III of the collaborative study included analyses of barriers to intervention and approaches that would facilitate the implementation of these interventions. This work, described above, led to controlled studies of implementation techniques (Saunders and Wutzke 1996; Gomel et al. 1998; and Funk et al. 2005). These studies examined the effectiveness of different promotional approaches to elicit interest in general practitioners in receiving materials to undertake screening and brief intervention. These studies conducted in six countries showed that direct mail techniques elicited a request for brief intervention materials among approximately half of general practitioners while telephone marketing and personal marketing (similar to pharmaceutical company academic detailing) had uptake rates of around 80 %. Thus, promotional techniques familiar to the commercial world could be adapted to the dissemination of brief alcohol interventions.

The next component of this work was to examine the effect of various training and support techniques in the actual provision of these interventions. Several such techniques were compared, with the end point being the proportion of patients with hazardous alcohol consumption who actually underwent screening and received an appropriate brief intervention. Results showed that among general practices where on-site training had been provided but where there was no subsequent training or support, approximately one-third of patients with hazardous consumption had received a brief intervention over the three-month period the study was being undertaken. On-site training followed by various levels of telephone-based support and personal contact resulted in up to 70 % of patients with hazardous consumption receiving an appropriate alcohol intervention.

Findings such as these would suggest that the widespread provision of training and subsequent support would be a successful means of incorporating screening and brief intervention into primary care. However, when an assessment was undertaken a year later, much of the screening and brief intervention had ceased. Medical practitioners typically reported they found the work interesting and they appreciated being involved in the study. However, in the absence of structural and contractual supports for brief interventions, their provision naturally tailored off and only approximately 10 % of practitioners were still providing them in any systematic way 1 year later.

Subsequent work has emphasized the importance of appropriate system of remuneration and also contractual obligation in the systematic provision of these interventions. An example is provided by the healthcare system of Scotland, United Kingdom, where general practitioners who work within the four regional health areas of Scotland have incentives and are obliged to undertake screening and brief alcohol interventions as part of the regions' contractual obligations with the Scottish Government. Overall, the level of acceptability of brief interventions with patients attending primary health care remains high. It is clear that the availability of screening and brief alcohol intervention in the healthcare system will be strongly influenced by government policy, as is translated into the contractual obligations of the healthcare system and healthcare providers.

Examples of policy recommendations and directives include the expectation that screening and brief intervention will be provided in all healthcare settings in Scotland (Scottish Intercollegiate Guidelines Network 2003), the recommendations of the US Preventive Services Task Force (US Preventive Service Task Force 2004), the guidelines published by the UK National Institute for Health and Clinical Excellence (NICE 2010), and the British Medical Association (BMJ Practice Guidelines 2011) and the National Preventative Health Taskforce, Australia (2009).

Opportunities for screening, early detection, and brief intervention for alcohol use disorders exist in many settings. These include general medical/family medical practice, other primary care settings (nurses, psychologists, social workers), emergency departments and acute care clinics, student health services, work place health programs, and also certain public areas such as shopping centers.

In addition to these primary care or community contact settings, brief interventions can be offered in hospital wards (general and psychiatric) and in a range of specialist services such as diabetes, hypertension, and liver clinics. There is mixed evidence for the effectiveness of brief intervention in hospital wards. These settings are of course quite diverse, and the extent to which a person can be engaged in any alcohol intervention will vary according to the primary task of a particular setting. Still, given that few people specifically request treatment and assistance in an alcohol use disorder, any attempt to identify these and to place them on the healthcare agenda is to be welcomed. In relation to setting, brief intervention has been demonstrated to be effective in primary care settings, emergency departments, hospital outpatient clinics and trauma centers.

Throughout this period, there has also been a tendency for patients who have actual alcohol use disorders to present for care at an earlier stage than was the case a generation ago. Furthermore, developments in general practice mean that questions on alcohol as well as cigarette smoking are more commonly part of the routine inquiry when patients attend primary care for the first time or are part of a periodic annual or biannual assessment. Even though the systematic approach of brief intervention may be less common than had been anticipated by those working in the area, nonetheless, in various areas of the world, it is more common for inquiry about alcohol use to be made.

12.2.5 Brief Intervention in Practice: The Techniques

1. FLAGS:

   Feedback: Problems experienced or likely to occur and link this with unhealthy drinking.

   Listen: Listen to the patient's response and assess his/her readiness to change (use motivational interviewing techniques as required) (Prochaska et al; 1992).

   Advice: Give clear advice to change and/or reduce unhealthy levels of drinking; list the benefits of change.

   Goals: Negotiate goals to reduce drinking to recommended limits.

   Strategies: Discuss practical methods and strategies, for example, how to determine at-risk times, and develop coping strategies.

2. FRAMES (brief intervention with motivational interviewing):

   Feedback: About personal risk and impairment.

   Responsibility: Emphasis on personal responsibility for change.

   Advice: To cut down, abstain if indicated because of severe dependence or harm.

   Menu: Menu of alternative options for changing drinking pattern and, jointly with the patient, setting a target; intermediate goals of reduction can be a start.

   Empathic interviewing: Listening reflectively without cajoling or confronting; exploring with patients the reasons for change as they see their situation.

   Self-efficacy: An interviewing style which enhances peoples' belief in their ability to change (Bien et al. 1993).

12.2.6 Development of Electronic Screening and Brief Intervention

In the recent years, we have witnessed an electronic revolution in communications. The advent of the Internet and the World Wide Web, the ready access electronically and wirelessly to the Internet, the vast array of information that can be stored electronically and be accessible, and the advent of lightweight laptop computers, tablets, smartphones, and the like mean that communication of information is easier than ever before. In addition, the potential interactivity that is possible electronically means that there can be a two-way flow of information between the person and an electronic store of information. In many areas of health care, this technology has been put to use for the provision of screening and assessment and the provision of relevant information and advice. Screening and brief intervention for alcohol use has been part of this.

Electronic screening and brief intervention has its origins in the late 1990s when the potential of the technology became apparent and also when there was interest in the widespread dissemination of health advice about alcohol. Soon, pioneering efforts in the provision of alcohol screening and brief intervention were made, and the first systematic studies appeared in the early 2000s (Kypri et al. 2003, 2004).

Electronic brief interventions have now been developed using a variety of platforms and have now achieved considerable popularity and population reach. Over the past 10 years, the use of the Internet as a means to access information – and advice – has become near universal in many countries, and even in many developing countries, 50 % of the population has access to the Internet. Technologies that have been adapted for electronic screening and brief interventions now include the older ones such as desktop computers, personal computers and laptops, touch screen instruments for use in community settings, and the new generation of smartphones, tablets, and other handheld instruments. Increasingly, people throughout the world are using these technologies as part of everyday life. The opportunities to adapt and utilize these technologies for screening and brief alcohol intervention are huge.

Screening and brief intervention has high levels of acceptability particularly among populations (such as young people) who are electronically literate. Studies among university and college students show acceptability levels exceeding 80 %, and receiving information electronically is more preferred among young people than receiving such information from a health professional.

Randomized controlled trials have shown electronic screening and brief intervention to result in significant changes in alcohol consumption and associated problems. A series of controlled studies in student populations, in both individual campuses and national studies, have shown significant effect sizes on measures of overall alcohol consumption, binge drinking, alcohol-related problems, measures of academic performance, and healthcare utilization. The effect size does appear to be slightly less for electronic interventions than that seen for clinician-provided interventions. However, given the high acceptability of electronic interventions and the potential reach to the at-risk population, electronic interventions have far greater capacity to be disseminated universally than could be achieved realistically through the dissemination of clinician-provided interventions.

More broadly, screening and brief intervention, including its electronic forms, offers the prospect of reducing alcohol-related harm at a population level as an alternative to primary prevention approaches based on control of per capita alcohol consumption. These latter approaches, although empirically sound, are difficult for governments to enact into effective policy as they impact on the availability and access to alcohol of the entire population and not just those whose drinking is hazardous and causing problems. In the modern world, governments have been reticent to impose tax imposts and restrictive legislation on alcohol consumption generally for fear of electoral unpopularity and economic considerations, particularly in those countries where the production of alcohol drinks is a significant part of the national economy. Screening and brief intervention therefore offers a population-wide and more politically acceptable approach to reducing harm from alcohol in the population at large. Both clinician-provided and electronic interventions have important roles to offer in the fulfillment of this goal.

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Screening for Nicotine and Drug Use Disorders

13

Sawitri Assanangkornchai and J. Guy Edwards

Contents

Abstract

Screening aims at detecting substance use, ideally at an early stage, with a view of providing subsequent treatment if required. It is most productively employed in populations in whom there is a high prevalence of use, such as general and

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emergency medical patients, those attending clinics for pain or sexually transmitted disorders, and people who have come into conflict with the law. It is of less value in well-staffed facilities that already routinely enquire about substance use during comprehensive clinical assessments.

Numerous screening instruments have been designed – those that screen for different substances in an aggregated or disaggregated way, those for one specific substance, and those for substance-related problems – but relatively few have satisfactory psychometric properties. Examples of instruments that screen for nicotine or drug use disorders or for multiple substances are the Alcohol, Smoking, and Substance Involvement Screening Test, CAGE-AID (mnemonic for items Cut down, Annoyed, Guilty, Eye-opener-Adapted to Include Drugs), Drug Abuse Screening Test, and the Fagerström Test for Nicotine Dependence. The choice of an instrument should depend on its psychometric properties, the population being screened, availability of staff to use it properly, and the practicality of introducing it into the facility.

Ethical aspects of the use of the instruments are important. Outside purely research settings, screening will have limited value unless follow-on treatment is available, and substance misusers are encouraged to accept it and adhere to it. The best test of the true value of screening will be in the prevention of Longer-term medical and psychosocial consequences of substance misuse.

13.1 Introduction

Screening for substance use and use disorders helps identify people who have suffered the consequences of using one or more substances or are at risk of future harm if they continue to use the substance(s). It aims to detect problems at an early stage and can be followed by treatment if indicated. Screening instruments for drug misuse have been evaluated in the community and health-care facilities and in relation to the law.

13.2 Facets of Drug Screening

13.2.1 Screening in Different Settings

13.2.1.1 Health-care Facilities

Screening may be undertaken in primary care; general and emergency medical, psychiatric, and other specialized facilities (e.g., HIV/AIDS, obstetric units); and community hostels. Some instruments are self-administered, and others administered by staff of various disciplines. Studies have shown the benefits of screening for drug use in various health-care settings as a first step in the public health approach in the Screening, Brief Interventions, and Referral for Treatment (SBIRT) process for illicit drug use (Babor et al. 2007).

13.2.2 Primary Care

Patients do not go to their doctors to be screened or rated, but to talk about their problems, to be listened to, and to receive treatment. In an ideal world, it should not be necessary to screen for substance use, because there would be adequately trained staff to carry out a comprehensive assessment that would "automatically" take all aspects of substance use into consideration. However, in the imperfect world in which we live – a world in which the demand for services greatly outstrips supply and conveyor-belt medicine is forced on us – screening offers a useful helping hand. It can also help educate personnel unfamiliar with substance misuse on the most important questions to ask and serve as an aide memoir for those who are already familiar with them.

Primary care deals with a wide range of people and an equally wide range of lifestyles and disorders, including substance misuse disorders. Its workers are usually seen as trustworthy, and it provides an excellent opportunity for early identification. We therefore endorse WHO recommendations on screening in general practice, with consideration given to the use of the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST; World Health Organization 2012) when time and/or staffing permits. Otherwise, shorter, simpler instruments should be used.

13.2.3 Secondary Care

13.2.3.1 General Medicine

Published evidence suggests that there is a high prevalence of substance use among general medical patients and that it is often associated with higher morbidity. Hospitals are therefore important places in which to screen patients, hoping that any substance misusers identified will accept treatment. In hospitals, there is more time for screening than in some other medical services and also more time to educate the patient about the relationship between substances misused and his/her medical condition (Mdege and Lang 2011).

13.2.3.2 Emergency Medicine

Drug misusers often attend accident and emergency departments with substance-related medical or surgical problems, notably toxic or withdrawal states, and trauma due to accidents, deliberate self-harm, or injury caused by others. Thus, emergency departments too are appropriate facilities to screen, especially for the benefit of people who have less access to alternative health care. However, because of the nature of the emergency department, where its workload is mostly stretched to capacity, screening may only be carried out with great difficulty or not at all without extra resources.

Notwithstanding these considerations, a systematic review showed that drug abuse screening in emergency departments is feasible. The study identified 11 instruments that have been used in youngsters under 21 attending these

departments and concluded that for cannabis this single question was sufficient: "In the past year, how often have you used cannabis?" with the response categories, "Once or less" or "Two or more times." The same question, reworded to screen for other drugs, might therefore be sufficient for them also (Newton et al. 2011).

13.2.3.3 Services for the Young and the Elderly

It is important to be vigilant for drug misuse in adolescents and young people and, at the other end of the age range, in elderly patients. Screening of children can be undertaken, subject to prevailing ethical and legal considerations, in schools, child welfare facilities, and the juvenile justice system (Center for Substance Abuse Treatment 1998). Screening should be with a valid, sensitive instrument, appropriate to the age group. When this suggests there is cause for concern, it should lead to a more comprehensive assessment. At all stages of the process, care should be taken not to label or stigmatize a young person as a drug misuser unjustifiably. Some drug types commonly used by adolescents or the elderly are of particular concern, for example, cannabis in the young and hypno-sedatives in the elderly.

13.2.3.4 Pain Clinics

Pain can be associated with drug misuse and dependence in several ways: there may be an underlying condition contributing to both the severity of the pain and the drug misuse (e.g., a depressive disorder); patients may become dependent on their prescribed analgesics (therapeutic dependence); and substance misusers with pain of organic origin, or with exaggerated or simulated pain, may try to manipulate their doctors into prescribing more addictive substances than are clinically needed – for themselves and/or to give or sell to other substance misusers. Whatever the relationship, screening patients attending pain clinics for inappropriate use is important. Because of the complexity of many of the disorders encountered there, however, no single instrument that is an adequate substitute for a thorough, comprehensive clinical assessment (Solanki et al. 2011).

13.2.3.5 Psychiatric Units

The prevalence of tobacco and other substance misuse is higher in patients with some mental health disorders than in others. Substance misuse and psychiatric comorbidity in general occurs so often it is essential that a history of substance use is taken routinely in all psychiatric patients. Indeed, failure to take a history can be a serious omission and in some cases may be considered negligent. Tiet and colleagues in their review concluded that there are no currently available instruments that have particular advantages in psychiatric patients, while the lengthier, more complicated ones can be confusing for those with severe illnesses – particularly when administered in addition to taking a long history (Tiet et al. 2008).

13.2.3.6 Other Specialities

Other units where screening is important are those in which there is a high prevalence of substance misuse, notably sexual health clinics and HIV/AIDS

services. Screening people attending antenatal clinics is also important, both because of the risk of adverse effects on the pregnant woman and on the fetus. Some screening questionnaires have been especially designed for this purpose, for example, the 4P's Plus, Hospital Screening Study (HSS), Substance Use Risk Profile-Pregnancy Scale (SURPPS), and Wayne Indirect Drug Use Screener (WIDUS) (ADAI Library 2013).

13.2.4 Medicolegal Practice

13.2.4.1 Criminal Justice System

There is a particularly high prevalence of substance misuse in people in conflict with the law, especially those whose alleged crimes have been carried out to acquire money for drugs. Screening in this setting poses particular ethical and legal issues. It is best undertaken by personnel working in prison medical services or in court diversion schemes. An aim of screening, in addition to providing treatment for those in immediate need, is to help interpret the cycle of addiction and drug-related crime, with benefits to society as well as to the drug misuser.

Screening should begin with simple questions regarding substance use. Opportunities for screening may include while the accused is in a police station, or in prison, and during pretrial investigations, meetings between prosecuting and defense counsel, and social assessments conducted by probation officers (Inciardi 1994).

13.2.5 Some General Considerations

13.2.5.1 Ethics

Even when using a simple screening instrument, it is important that we remain aware of the concerns and sensitivities of our patients/clients, concerns such as embarrassment or fear of the legal and other social consequences of drug use. It is essential that honesty and transparency are central to our dealings with patients.

Patient's anxieties can be allayed by emphasizing that the decision to reveal information in response to questions asked by the instrument is theirs and theirs alone. In health-care settings, the patient should be assured that anything revealed will be treated in strict confidence and not disclosed to others without their permission. In the justice system, the extent to which information will be disclosed to others will need to be made explicit. Doing this is particularly important in medicolegal work, whether in civil or criminal cases, and especially so when dealing with delinquent youngsters to help gain their trust, confidence, and cooperation.

13.2.5.2 Psychometric Properties

All instruments employed should be properly constructed and evaluated, and then administered appropriately. Even when these principles have been conscientiously adhered to, there remains the possibility that the information provided by the respondent may be inaccurate.

13.2.5.3 Main Aims of Screening

While it is of interest academically to elicit data on all substance use, clinicians will generally be less interested in people who occasionally experiment with substances (especially if this is common in the peer group) or take them only in certain situations, like parties, clubs, or raves. Although clinicians may need to advise people of the dangers of sporadic or short-lived periods of drug taking, their main focus will be on more regular and/or prolonged substance use. This is especially the case when the person is dependent on one or more substances, has already experienced medical or psychosocial problems due to the substance, or is exposed to the risk of these problems in the future.

There are debates on what are the differences between use, misuse, and abuse and when psychological and/or physical dependence begins. These are of theoretical and practical interest, but matter less at the screening stage than later in assessment. The main aim at this stage is to identify people who have or are at risk of substance-related problems and may therefore benefit from advice and/or intervention regardless of what provisional labels are applied to them.

Having done the screening the clinician, aided by the data elicited by the screening instrument, may then complete the assessment, make a diagnosis, and provide the appropriate intervention.

13.2.6 Screening Instruments for Tobacco and Drug Use Disorders

Screening instruments for substance use disorders are categorized into four groups: instruments that enquire about different types of drugs in a disaggregated way, enquire about drug use in an aggregated way, are specific to one drug, and enquire about multiple problems, including comorbidity (Table 13.1).

13.2.7 Instruments Enquiring About Different Drug Types in a Disaggregated Form

Examples in this group include the WHO Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) and its modified forms and the Drug History Questionnaire (DHQ).

13.2.7.1 ASSIST

The ASSIST is a screening instrument developed by a group of WHO researchers to help detect substance use and related problems in primary and general medical care. It can help health workers identify the level of risk for each substance identified. It seeks information on the use of all types of psychoactive substances, including tobacco, alcohol, cannabis, cocaine, amphetamine-type stimulants, sedatives, hallucinogens, inhalants, and opioids. It asks if any of these have ever been used and, if so, the frequency of use during the past three months; if the respondents have had a strong desire or urge to use the substance; the frequency of any problems they

Table 13.1 Screening instruments for drug use and drug use disorders

Instrument	Full name	References	Population studied	Time frame	No. of items	Administered by	Approx. time required	Score
(a) Instruments enquiring about different drug types in a disaggregated form								
ASSIST	Alcohol, Smoking and Substance Involvement Screening Test	World Health Organization (2002)	Adults	Lifetime Past 3 months	8 items	Clinician-administered interview Computer-administered format available Adolescent version available	10 min for administration, 5 min for scoring	0–3: low risk, no intervention (0–10 for alcohol) 4–26: moderate risk, brief intervention (11–26 for alcohol) 27+: high risk, more intensive intervention
DHQ PDHQ	Drug History Questionnaire Psychoactive Drug History Questionnaire	Sobell et al. (1995)	Adults	Lifetime Past 6 months	5 items	Self-administered	5–10 min	No specific cutoff
(b) Instruments enquiring about drug use in an aggregated form								
CAGE-AID	Cut down, Annoyed, Guilty, Eye-opener-Adapted to Include Drugs	Brown and Rounds (1995)	Adolescent; patients with comorbidity; adults	Lifetime	4 items	Self-administered	5 min	Range: 0–4 Cutoff score 1 or more for drug dependence
CRAFFT RAFFT	Car, Relax, Alone, Forget, Friends, Trouble	Knight et al. (1999)	Adolescents American Indian/native Alaskans	Lifetime Past year	6 items	Interviewed, self-administered, computerized	5 min	Range: 0–6 Cutoff score of $\geq$2 for risky use
DAST	Drug Abuse Screening Test	Skinner (1982)	Adults College students; pregnant women	Lifetime	10, 20, 28 items	Self-administered Adolescent version (DAST-A) available	5–10 min	Range: 0–10, 20, 28 DAST-28: cutoff 6 DAST-20: cutoff 6 DAST-10: cutoff 2

(*continued*)

Table 13.1 (continued)

Instrument	Full name	References	Population studied	Time frame	No. of items	Administered by	Approx. time required	Score
DAP Quick Screen DAP-4	Drug and Alcohol Problem Quick Screen	Schwartz and Wirtz (1990)	Adolescents	Lifetime	30 items & 4 items	Self-administered	<10 min	Range: 0–30 Score of ≥6 considered high risk for "red flag" behaviors
DUDIT	Drug Use Disorder Identification Test	Berman et al. (2005)	Adults	Lifetime Past year	11 items	Self-administered	5–10 min	Range: 0–44 Cutoff score of 25 suggestive for substance dependence Cutoff score of 8 for less severe drug abuse
SACS	Substances and Choice Scale	Grant et al. (2007)	Adolescents	Past month	10 items	Self-administered	5–10 min	Each item scores 0, 1, 2 for not true, somewhat true, certainly true Range: 0–20 Cutoff: 2
SSI-SA SSI-SOA SSI-AOD	Simple Screening Instrument for Substance Abuse, Simple Screening Instrument for Alcohol and Other Drug Abuse	Winters et al. (1994)	Adults; patients with comorbidity; correction-based drug treatment programs, adolescent, medical patients	Lifetime	16 items	Clinician-administered interview Self-administered questionnaire	10 min	0–1: non/low risk 2–3: minimal risk 4+: moderate/high risk

TICS[a]	Two-Item Conjoint Screen for Alcohol and Other Drug Problems	Brown (1997)	Adults	Past year	2 items	Self-administered	≤5 min	Cutoff: 1
UNCOPE	Use, Neglected, Cut down, Objection, Preoccupied, Emotional discomfort	Hoffmann et al. (2003)	Adults	Lifetime Past year	6 items	Interviewer administered	5–10 min	Cutoff: 2
(c) Instruments specific to one drug								
CAST	Cannabis Abuse Screening Test	French Monitoring Center for Drug and Drug Addictions (2013)	Adolescents	Lifetime	6 items	Self-administered	≤ 5 min	Range: 0–6 Score ≥ 4: problematic cannabis use
CUDIT CUDIT-R	Cannabis Use Disorders Identification Test	Adamson et al. (2010), Adamson and Sellman (2003)	Adults; adolescents	Past 6 months Current	10 items 5-point Likert scale	Self-administered	5–10 min	Range: 0–40 Cutoff:8
CUPIT	Cannabis Use Problems Identification Test	Bashford (2010)	Adolescents; adults	Lifetime Past 12 months	16 items	Self-administered	5 min	Range: 0–82 Cutoff: 12
MSI	Marijuana Screening Inventory	Alexander (2003)	Adults	Lifetime Past year	31 items	Self-administered	5–10 min	Range: 0–31 Cutoff: 3
PUM	Problematic Use of Marijuana	Piontek et al. (2008)	General adult population	Lifetime	8 items	Self-administered		Range: 0–8 Cutoff: 2
CDS-12 CDS-5	Cigarette Dependence Scale	Etter et al. (2003)	Adults Adolescents	Lifetime Current	12 & 5 items	Self-administered	10 min	Range: CDS-12, 12–60; CDS-5, 5-25

(*continued*)

Table 13.1 (continued)

Instrument	Full name	References	Population studied	Time frame	No. of items	Administered by	Approx. time required	Score
FTND FTQ m-FTND	Fagerström Test for Nicotine Dependence Fagerström Tolerance Questionnaire Modified Fagerström Tolerance Questionnaire	Heatherton et al. (1991) Prokhorov et al. (1998)	Adults Adolescents College students	Lifetime	6 items	Clinician-administered interview; Self-administered	≤5 min	Range: 0–2 Cutoff: 6
TDS	Tobacco Dependence Screener	Kawakami et al. (1999)	Adults; smokers	Lifetime	10 items	Self-administered	5 min	Range: 0–10 Cutoff: 6
COMM	Current Opioid Misuse Measure (for opioid medication misuse)	Butler et al. (2007)	Adult patients with chronic noncancer pain	Current Past 30 days	17 items	Self-administered	5–10 min	Cutoff:9
ORT	Opioid Risk Tool	Webster and Webster (2005)	Adult patients prescribed opioids for chronic pain	Lifetime	5 items	Patient-completed (PC-ORT) Clinician-completed (CC-ORT)	5 min	Range: 0–16 Cutoff: 0–3, low risk 4–7, moderate risk ≥ 8, high risk
SOAPP	Screener and Opioid Assessment for Patients with Pain	Butler et al. (2004)	Adult patients taking opioids for chronic pain	Lifetime	5, 14, or 24 items	Self-administered	5–10 min	Cutoff: >7

(d) Instruments enquiring about multiple problems, including dual diagnosis								
CODSI-MD CODSI-SMD	Co-occurring Disorder Screening Instrument	Sack et al. (2007)	Offenders	Past 12 months	6-item version (CODSI-MD) screens for any mental disorder 3-item version (CODSI-SMD) screens for severe mental disorder	Self-administered	5–10 min	CODSI-MD Range: 0–6 Cutoff: ≥3 CODSI-SMD Range: 0–3 Cutoff: ≥2
DUSI[b]	Drug Use Screening Inventory – Revised	Tarter (1990)	Adults; adolescents	Current status	159 items	Self-administered Computer-based available	20–40 min	Range: 0–100 % No cutoff specified in documents
PL	Drug Check Problem List	Kavanagh (2011)	Adolescents; adults; co-occurring clients	Past 3 months	12 items	Clinician interviewed	5-10 min	Range: 0–12 Cutoff: ≥2
POSIT	Problem-Oriented Screening Instrument for Teenagers	Rahdert (1991)	Adolescents	Lifetime	139 items, 10 problem areas	Self-administered	20–30 min	Cutoff scores indicating low, medium, or high risk for each of the 10 problem areas

[a]Copyright information unavailable
[b]Fee required for use; other instruments free in public domain

have had; if the substance has interfered with their responsibilities; if anyone has expressed concern about their substance use; if they have tried to decrease or discontinue use; and if they have ever used any substance by injection (WHO ASSIST Working Group 2002).

There are modified forms of the ASSIST – the NMASSIST (National Institute on Drug Abuse (NIDA)-modified ASSIST) (National Institute on Drug Abuse 2013); ASSIST-Lite (ultrarapid ASSIST) (Ali et al. 2013); ASSIST-Y for use in children and adolescents aged 10–17 years; and the electronic eASSIST (Drug and Alcohol Services South Australia (DASSA) 2012).

In a validation study among 1,047 participants in drug treatment and primary health-care settings in Australia, Brazil, India, Israel, Thailand, the UK, the USA, and Zimbabwe, the ASSIST showed high construct and concurrent validity and positive correlation with similar instruments ranging from 0.48 to 0.88 ($p < 0.001$) (Humeniuk et al. 2008). The sensitivity in the study ranged from 54 % to 97 %, specificity 50–96 %, depending on the drug type. The instrument was later tested in 214 patients with first episode psychoses and revealed satisfactory concurrent validity ($r = 0.41–0.63$; $p < 0.001$), with a sensitivity of 63–81 % and specificity of 62–76 % (Hides et al. 2009). Both studies also showed high validity in discriminating between nonproblematic use, abuse, and dependence and between those with and without illicit drug problems. A high internal consistency and good-to-excellent test–retest reliability (kappa, 0.58–0.90) were also reported (WHO ASSIST Working Group 2002). In a diagnostic accuracy study among 2,082 adults recruited from general medical and specialist mental health/addiction treatment services in nine countries, the ASSIST-LITE also showed high sensitivity (0.8–1.0) and specificity (0.7–0.8) (Ali et al. 2013).

13.2.8 Instruments Enquiring About Drug Use in an Aggregated Form

This group of instruments enquires about experiences of all drugs, including alcohol and tobacco. The word "drugs" is used in the questionnaire without reference to any specific substance. For example, a question in the CAGE-AID asks "Have you ever felt that you ought to cut down on your drinking *or drug use*?" Screening questionnaires of this type are not only quick to administer, but they also have the advantage that people who use multiple substances may be more likely to respond positively to a conjoint question than to questions about each specific drug. However, they have some disadvantages. For example, someone who uses only alcohol may not respond in the affirmative to a question that includes drugs. Also, conjoint questions do not detect specific substances. Examples of instruments of this type are CAGE-AID (Cut down, Annoyed, Guilty, Eye-opener – Adapted to Include Drugs), CRAFFT/RAFFT (below), the Drug Abuse Screening Test (DAST), and the Substance Abuse Subtle Screening Inventory (SASSI).

13.2.8.1 CRAFFT

CRAFFT is a mnemonic, based on its individual items: Car, Relax, Alone, Forget, Friends, and Trouble (Knight et al. 1999). It is the best studied instrument for screening for alcohol and drug use and related problems in adolescents (Pilowsky and Wu 2013). The six items are preceded by three preliminary questions that ask about the use of alcohol, cannabis, and other drugs. It evaluates certain lifetime events and behaviors, irrespective of when they occurred. The items were developed from the Problem-Oriented Screening Test for Teenagers (POSIT), Drug and Alcohol Problem (DAP) Quick Screen, and RAFFT questionnaire (Relax, Alone, Forget, Friends, Trouble). The CRAFFT was examined in several populations, including patients seen in hospital-based, sexually transmitted disease and substance use clinics, primary care, emergency departments, and the general population. The instrument was found to be suitable for distinguishing between alcohol and substance use, and problem use, abuse, and dependence, with a sensitivity ranging from 0.61 to 1.00, specificity from 0.33 to 0.97 (Dhalla et al. 2011).

13.2.8.2 Drug Abuse Screening Test (DAST)

The DAST-28 is an instrument used for screening and treatment evaluation research. Responses to the DAST are given as binary (0/1) items, yielding a total score ranging from 0 to 28. A cutoff score of 6 is generally used to indicate drug abuse or dependence (Yudko et al. 2007). It provides a measure of the severity of drug-related and other problems experienced during the respondent's lifetime. It has been used in various populations and has been found most useful in people who do not seek treatment.

The original test was adapted from the MAST (Michigan Alcoholism Screening Test), a screening instrument for problematic alcohol use. Like the MAST, the DAST cannot distinguish between active or inactive drug use or abstinence and low-risk use, abuse, or dependence. Alternate versions of the DAST-28 have been developed – the DAST-20, DAST-10, and DAST-A (for adolescents). DAST has moderate to high test–retest, inter-item and item–total reliability, sensitivity (41–96 %), and specificity (68–99 %), depending on the group studied (Yudko et al. 2007).

13.2.9 Instruments Specific to One Drug

Apart from instruments used to screen for alcohol, those most readily available are for cannabis, tobacco, and opioid use. Short instruments designed specifically for cannabis screening that have satisfactory psychometric properties and have been used in various populations include the Cannabis Abuse Screening Test (CAST), Cannabis Use Disorders Identification Test (CUDIT), and Problematic Use of Marijuana (PUM) (Piontek et al. 2008). The Fagerström Test for Nicotine Dependence (FTND) is the instrument most widely used to screen for nicotine use, while other available instruments are the Cigarette Dependence Scale (CDS) and Tobacco Dependence Screener (TDS). For opioids, most instruments, such as the Current

Opioid Misuse Measure (COMM), Opioid Risk Tool (ORT), and Opioid Assessment for Patients with Pain (SOAPP), were designed to elicit information to identify patients with chronic pain who are at risk of problems caused by their long-term analgesic treatment.

13.2.10 The Fagerström Test for Nicotine Dependence

The Fagerström Test for Nicotine Dependence (FTND) is also known as the Fagerström Test for Cigarette Dependence (FTCD), a revision of the Fagerström Tolerance Questionnaire (FTQ). It was designed to provide an ordinal measure of nicotine dependence. It contains six items that seek information on the number of cigarettes smoked, compulsion to smoke, and dependence. It provides a severity rating that can be used to help plan treatment and assess the prognosis. Its brevity and ease of scoring make it an efficient way of obtaining clinically meaningful information. It can be incorporated into general health and lifestyle screening questionnaires for use in clinical and nonclinical settings.

A modified version of the scale (modified Fagerström Tolerance Questionnaire, mFTQ) has been adapted for use in adolescents. The FTND was found to be reliable for evaluating smokers in different settings. It had a test–retest reliability ranging from 0.58 to 0.91, with the lowest value in smokers with schizophrenia, and a sensitivity of 0.75 and specificity of 0.80 in a study among patients with cancer in Japan. There was a weak ($r = 0.19$) to satisfactory ($r = 0.59$) correlation between the FTND score and breath carbon monoxide and saliva cotinine levels (Meneses-Gaya et al. 2009).

13.2.11 Instruments Enquiring About Multiple Problems, Including Comorbidity

These instruments help identify drug-related problems in mental and physical health, relationships, and adjustment at school or work. They may locate areas in need of further assessment and suggest services required. Examples include the Co-occurring Disorder Screening Instrument (COMM), Drug Use Screening Inventory – Revised (DUSI-R), Drug Check Problem List (PL), and Problem-Oriented Screening Instrument for Teenagers (POSIT).

13.2.11.1 Problem-Oriented Screening Instrument for Teenagers (POSIT)

The POSIT is a self-administered 139-item questionnaire, with fixed "yes/no" responses, designed for use in adolescents aged 12–19 (Rahdert 1991). It identifies problems in 10 domains that require further assessment and might need the provision of services; these domains include substance use/abuse, mental and physical health, family and peer relations, vocation, and special education. The instrument can be used by school personnel, juvenile and family court personnel, medical and

mental health-care staff, and staff working in substance use disorder treatment programs. The POSIT has been found to have strong internal consistency in several of its subscales and good test–retest reliability and overall validity (Knight et al. 2001, 2003).

13.3 Conclusion

Because of the high and increasing prevalence of substance use disorders and related comorbidity, screening for substances is important in many medical, psychiatric, and forensic services. There is a higher prevalence of use in some patient groups than others, such as those attending accident and emergency departments and pain clinics, and those who come into conflict with the law. Numerous screening instruments have been designed and validated. Factors that determine the choice of an instrument are not only its psychometric properties but also the practicality of employing it. The enormous pressures of working in a busy clinical unit often preclude the use of the lengthier instruments without special assistance. It should not be forgotten that screening is only the first step on a very long journey towards providing a successful outcome. It will be of limited value without the provision of treatment opportunities and encouraging substance users to accept and then adhere to any treatment offered. Finally, it is important to determine the success rate of using the instruments in terms of discontinuation or at least decreased use of substances compared with standard practice and to assess what effect they have in reducing long-term complications.

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Clinical Assessment of Alcohol Use Disorders

14

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Contents

Abstract

Clinical assessment of alcohol use disorders involves both a detailed initial interview and examination and monitoring of the patient's progress. There are no specific instruments to diagnose alcohol misuse, and so diagnostic assessment involves taking an accurate history from the patient and a meticulous clinical

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examination. This chapter reviews the necessary attributes of a detailed clinical assessment, namely, (1) utility and purpose (screening, diagnosis, treatment planning, outcome evaluation), (2) time frame (current vs. chronic use), (3) specific target subgroup (age, gender, inpatient vs. outpatient, ethnicity), and (4) performance characteristics and adequate psychometric properties regarding validity and reliability. It also provides a description of the most relevant psychometric instruments to evaluate alcohol use disorders and related problems (historical and recent patterns of drinking; dependence and withdrawal symptomatology; craving and impulsiveness; legal, economic, and occupational problems; coping behaviors and confidence in relapse prevention; readiness to change), psychiatric comorbid symptomology (global and specific mental health measures), neurocognitive performance, social functioning, and quality of life and disability issues.

14.1 Introduction

Alcohol use disorders range from periodic consumption of hazardous quantities of alcohol to a pattern of drinking that is causing personal and health problems through to a disorder where the person is essentially disabled because of incessant drinking and recurrent withdrawal states. The starting point of assessment is to undertake screening and brief assessment so that the type and severity of alcohol use disorder is identified. This initial phase is addressed in a companion chapter in this book (see ▶ Chap. 12, "Screening, Early Detection and Brief Intervention for Alcohol Use Disorders").

After a person has been detected and diagnosed, an in-depth assessment, which involves both integrative comprehension of the patient and monitoring of the patient's progress, is needed. Ongoing assessment and monitoring is important because clients' symptoms and functioning may change throughout treatment, and so will priorities and targets of intervention. For instance, a patient may report anxiety symptoms or dysphoric mood upon entry into treatment and have these symptoms attenuated after achieving abstinence. By the same token, another person could enter treatment with apparently no mental health symptomatology but develop them after a period of reduced use, if he (or she) had been self-medicating with alcohol (Deady 2009). At the same time, it should be noted that recent alcohol abuse may influence neuropsychological performance, psychiatric symptomatology, and social and personal functioning, so it is strongly recommended to conduct further evaluations to determine a better approach of patient's underlying mental health and cognitive performance. It is fundamental to bear in mind that the primary benefit of assessment is not only to accurately and efficiently determine the treatment needs of the patient but also to build rapport. For this reason, it is the heart of the assessment to avoid confrontational approaches and adopt a motivational one instead (see ▶ Chap. 47, "Motivational Interviewing and Behaviour Change in Addiction Treatment").

An all-embracing evaluation should appraise multiple domains of need and explore the following areas:

- Alcohol consumption:
  - Historical and recent patterns of drinking
  - Dependence and withdrawal symptomatology
  - Alcohol craving and impulsiveness
  - Alcohol-related problems (i.e., legal, economic, occupational)
  - Self-efficacy and confidence in relapse prevention
  - Readiness to change
- Other drug misuse, including prescribed and under-the-counter medication
- Comorbid mental health disorders
- Comorbid physical health conditions
- Neurocognitive performance
- Social and personal functioning
- Quality of life and disability

This information may be obtained by a precise clinical interview, but standardized tools and measures may be administered as well (see Table 14.1).

This chapter will enumerate and briefly describe the most relevant psychometric instruments to evaluate alcohol use disorders and related problems, psychiatric comorbid symptomology, neurocognitive performance, and social functioning and quality of life issues. The reader is recommended to consult the companion ▶ Chap. 12, "Screening, Early Detection and Brief Intervention for Alcohol Use Disorders" and ▶ Chap. 15, "Drug Testing" for further information about complementary methods of assessment. Regarding physical and mental health comorbidities, Section VIII is an exhaustive revision on ▶ Medical Disorders and Complications of Alcohol and Other Drugs, Pain and Addiction, and Section IX addresses ▶ Psychiatric Comorbidities and Complications of Alcohol and Other Drugs.

14.2 Comprehensive Assessment of Alcohol Use and Related Problems

14.2.1 Evaluation of Alcohol Use

There are no specific instruments to diagnose alcohol misuse, so fundamental diagnostic methods consist of an accurate history from the patient and a thorough clinical examination. Notwithstanding this fact, psychometric tools are of considerable aid to appraise addictive disorders when used by trained specialists.

14.2.1.1 Clinical Severity of Addiction

Addiction Severity Index

The ASI is a semi-structured interview designed to address seven potential impairments and problem areas in substance-abusing patients: medical conditions, employment and support, drug use, alcohol use, legal issues, family/social relationships, and psychiatric disorders. It consists of 200 items, which gather information on recent (past 30 days) and lifetime problems in all of the problem areas. Last version (ASI 6.0) (Cacciola et al. 2011; McLellan et al. 2006) is composed of

Table 14.1 Distinctive features in instrument selection

Feature	Characteristics
Clinical utility	Screening
	Diagnosis
	Assessment of drinking behavior
	Treatment planning
	Intervention monitoring
	Outcome appraisal
Time frame	Recent/short-term/current use versus chronic/long-term/ lifetime use
Specific subgroup	Adolescent, adult, elderly
	Women (pregnant)
	Imprisoned
	Homeless
	Inpatient versus outpatient
	Cultural issues/ethnicity
Sensitivity/positive predictive value (PPV)	Proportion of patients with the condition correctly classify as "diseased"
Specificity/negative predictive value (NPV)	Proportion of individuals without the condition who are correctly classified as "disease-free"
Validity (test measures what is intended to measure)	Content (comprehensiveness)
	Construct (conceptual components, internal structure)
	Convergent (similar to other tests to assess that construct)
	Discriminant (different to tests that assess other constructs)
	Criterion (correlation with gold standard measures)
	Concurrent (similar measures obtained to comparative tests at same time frame)
	Predictive (ability to predict future outcome)
Reliability (accuracy of assessment)	Test-retest (correlation at two different time points)
	Inter-rater (degree of agreement by different raters)
	Internal consistency (items of test measure same aspect)

15 scales: 9 primary scales (related to main problem areas) and 6 secondary scales (perceived support and conflicts with partner, family, and friends) (McLellan et al. 1980). There is a follow-up version (ASI-FU follow-up) designed to monitor patients' evolution and treatment outcomes and several adaptations to adolescent population: Teen-ASI (Kaminer et al. 1989) and T-ASI-2 (Brodey et al. 2008).

Alcohol Use Inventory

The AUI is a self-administered instrument which includes 24 scales that intend to describe different ways in which individuals use alcohol, benefits and negative consequences derive from such use, and awareness and readiness for help (Horn et al. 1987). It consists of 228 items grouped in primary scales regarding benefits, styles, consequences, and concerns and acknowledgments of alcohol use and other second-order factor scales.

Comprehensive Drinker Profile

The CDP is a structured interview that contains 88 questions inquiring different areas of interest: alcohol use, everyday problems, most common drinking settings, people with whom they drink, beverage preferences, reasons for drinking, effects and life problems related to alcohol use, and patient's concerns and issues (Miller and Marlatt 1984). Three instruments were derived from the CDP: the Brief Drinker Profile (BDP), the Follow-up Drinker Profile (FDP), and the Collateral Interview Form (CIF).

14.2.1.2 Dependence/Withdrawal Symptoms

Severity of Alcohol Dependence Questionnaire

The SADQ is a self-administered questionnaire designed to measure severity of dependence (Stockwell et al. 1979). There are four items in each of the five scales that gather information on a 6-month time frame: physical withdrawal, affective withdrawal, withdrawal relief drinking, alcohol consumption, and rapidity of reinstatement. Scores range between 0 and 60 points, and scores greater than 30 are suggestive of severe alcohol dependence. It has demonstrated adequate content and criterion (predictive) validity and test-retest reliability.

Alcohol Dependence Scale

The ADS consists of 25 items that interrogate alcohol withdrawal symptoms, impaired self-control over drinking, awareness of compulsive drinking, tolerance to alcohol, and salience of drink-seeking behavior (Skinner and Allen 1982; Skinner and Horn 1984). It has shown good predictive value, content and construct validity, and test-retest and internal consistency reliabilities. A computerized version is also available. It is an adequate instrument for clinical and research purposes.

Short Alcohol Dependence Data

This 15-item instrument was derived from the Alcohol Dependence Data (ADD) in order to accomplish an easier and faster measure profitable for seeking-help patients, current state dependence assessment, sensitive to change over time, and free of cultural influences. It can be self-administered or interviewer administered in about 2–5 min and has good reliability and validity parameters (Raistrick et al. 1983).

Clinical Institute Withdrawal Assessment

The CIWA-AD is an 8-item scale for clinical quantification of the severity of the alcohol withdrawal syndrome (Sullivan et al. 1989). It is useful to monitor patients undergoing alcohol withdrawal as it focuses on both intensity and severity of symptoms. Scores over 20 indicate a severe withdrawal syndrome, and inpatient detoxification is strongly recommended.

14.2.1.3 Craving/Impulsiveness

The Obsessive Compulsive Drinking Scale

The OCDS is a 14-item scale developed to reflect obsession and compulsion related to craving and drinking behavior such as drinking-related thoughts, urges to drink,

and the ability to resist those thoughts and urges (Anton et al. 1995). The OCDS has been shown to be a reliable and sensitive as a monitoring tool and has proved content and predictive validity for relapse drinking. There is an adolescent version, the A-OCDS (Deas et al. 2001), which discriminates between problem drinkers and experimenters and detects functional impairment associated with alcohol abuse.

Penn Alcohol Craving Scale

The PACS is a five-item self-administered instrument for assessing frequency, intensity, and duration of thoughts about drinking and the ability to resist drinking (Flannery et al. 1999). Although it was intended for adults, it may be used in adolescent population. Good reliability and validity measures have been obtained.

Alcohol Craving Questionnaire

The ACQ-NOW is a 47-item self-administered, multidimensional state measure of acute alcohol craving (Singleton et al. 1995). It measures four dimensions: emotionality, purposefulness, compulsivity, and expectancy. There is a 12-item short form, the ACQ-SF-R. It has demonstrated adequate reliability and is sensitive to change.

Impulsive Behavior Scale

The UPPS is a 45-item scale designed to measure impulsivity across dimensions of the Five-Factor Model of personality (Whiteside and Lynam 2001). It measures 4 domains: premeditation, urgency, sensation seeking, and perseverance. The revised version, UPPS-P, consists of 59 items and assesses an additional personality pathway to impulsive behavior, positive urgency (Cyders et al. 2007).

Barratt Impulsiveness Scale

The BIS is one of the oldest and most widely used measures of impulsive personality traits (Barratt 1959; Patton et al. 1995). The last version, BIS-11, contains 30 items grouped in three subscales: attentional impulsiveness, motor impulsiveness, and non-planning impulsiveness. This scale is intended to measure six factors: attention, motor impulsiveness, self-control, cognitive complexity, perseverance, and cognitive instability.

14.2.1.4 Self-Efficacy and Expectancy

Alcohol Abstinence Self-Efficacy Scale

The AASE was designed to evaluate self-efficacy in 20 situations that represent typical drinking cues associated to negative affect; social/positive, physical, and other concerns; and withdrawal and urges (DiClemente et al. 1994). It may be also used to assess an individual's temptation to drink. It has shown great utility to intervene over relapse potential situations, monitor progress in treatment, and assess outcomes.

Drinking Refusal Self-Efficacy Questionnaire

The DRSEQ is a 31-item measure of drinking-related self-efficacy (Young and Oei 1991). It is grouped in three factors: drinking in situations characterized by social

pressure, opportunistic drinking, and emotional relief. Adequate reliability and validity have been analyzed.

Alcohol Expectancy Questionnaire

The AEQ is an empirically derived self-report form designed to assess the domain of alcohol reinforcement expectancies (Brown et al. 1987). It consists of six subscales: positive global changes in experience, sexual enhancement, social and physical pleasure, assertiveness, relaxation/tension reduction, and arousal/interpersonal power. Total scores are predictive of current and future drinking practices, persistence and participation in treatment, and relapse following treatment.

Negative Alcohol Expectancy Questionnaire

The NAEQ is a 60-item questionnaire that assesses the extent to which negative consequences are expected to occur if that person were to "go for a drink now" (McMahon and Jones 1993a, b). The expected negative consequences are held to represent motivation to stop drinking. There are three different time frames: same day, next day, and long-term expected consequences. Responses are measured in terms of how likely it is that a person would expect them to occur and are measured on a 5-point Likert scale. A short version composed of 22 items is also available. This instrument is very useful at intake and during treatment to intervene over motivational factors during therapeutic process.

14.2.1.5 Motivation to Change

University of Rhode Island Change Assessment

The URICA is a 32-item self-report measure used to assess motivation for change that includes four subscales: precontemplation, contemplation, action, and maintenance (McConnaughy et al. 1983). These subscales can be combined in order to yield a second-order continuous readiness to change score (C + A + M-PC). It has demonstrated adequate internal consistency as well as content and criterion validity.

Readiness to Change Questionnaire

The RCQ is comprised of 12 items and focuses on readiness to change drinking behavior (Rollnick et al. 1992). It is based on the URICA questionnaire and is founded on Prochaska and DiClemente's theory on stages of change. It is clustered into three factors: precontemplation, contemplation, and action. It has good psychometric properties, including predictive validity. There is a treatment version, the RCQ (TV), for use in patients at treatment settings.

Stages of Change Readiness and Treatment Eagerness Scale

The SOCRATES consists of 40 items grouped in five stages of change: precontemplation, contemplation, determination/preparation, action, and maintenance (Miller and Tonigan 1996). The SOCRATES 8A is a 19-item version that yields three factorial-derived scale scores: recognition, ambivalence, and taking steps. There are other available forms of the SOCRATES: 8D 19-item drug/alcohol questionnaire for clients, 7A-SO-M 32-item alcohol questionnaire for significant

others of males, 7A-SO-F 32-item alcohol questionnaire for SOs of females, 7D-SO-F 32-item drug/alcohol questionnaire for SOs of females, and the 7D-SO-M 32-item drug/alcohol questionnaire for SOs of males. These SO forms are intended to measure motivation for change of significant others (rather than patient's motivation).

14.2.2 Psychiatric Comorbidity Assessment

Individuals with alcohol use disorders often suffer from one or more psychiatric disorders. This frequent phenomenon indicates the necessity of specific assessment and treatment in the field of addictive behaviors, which, historically, has been narrowed and focused on the addiction per se. This section yields over basic instruments to assess psychiatric comorbidity in patients with alcohol problems (see Table 14.2). For further information on psychiatric comorbidity, consult section IX of this book, ▶ Psychiatric Comorbidities and Complications of Alcohol and Other Drugs.

14.2.3 Neuropsychological Performance

Studies have long established that excessive alcohol use is associated with damage and impairment of brain structure and function, yielding to poor cognitive performance and behavior disturbances. Assessment of neuropsychological performance (and intervention where necessary) is fundamental, given that it determines assimilation and understanding of information, reasoning, and problem solving (in order to prevent relapse) and capacity to remember therapeutic guidelines, learn new skills, maintain abstinence, and develop more adaptive behaviors. This section enumerates the most relevant tests to evaluate neuropsychological performance (see Table 14.3).

14.2.4 Psychosocial Functioning and Quality of Life

Alcohol and other drug use disorders are increasingly viewed as chronic conditions. It is therefore important to assess their impact on the patient's overall well-being. From this perspective, the management of addictive behaviors should aim for the broad goal of recovery, which is defined as abstinence plus improved quality of life and psychosocial functioning. Assessing these social parameters is essential in treatment planning and outcome assessment as they represent the abilities and skills of the individual to function independently in the community.

14.2.4.1 Disability

Disability Assessment Schedule 2.0

The WHODAS 2.0 was developed through a collaborative international approach, with the aim of developing a single generic instrument for assessing health status and disability across different cultures and settings (World Health Organization 2010). It is short, simple, and easy to administer and one first-level general

Table 14.2 Psychometric instruments to evaluate psychiatric comorbidity

Construct	Instrument	Author
Psychiatric comorbidity	Psychiatric Research Interview for Substance and Mental Disorders (PRISM)	(Hasin et al. 1996)
	Composite International Diagnostic Interview (CIDI)	(World Health Organization 1990)
General symptoms	Symptom Checklist-90-Revised (SCL-90-R)	(Derogatis and Cleary 1977)
	Minnesota Multiphasic Personality Inventory (MMPI-2)	(Mc Kinley et al. 1948)
Affective symptoms	Hamilton Depression Rating Scale (HDRS)	(Hamilton 1960)
	Beck Depression Inventory-II (BDI-II)	(Beck et al. 1996)
	Young Mania Rating Scale (YMRS)	(Young et al. 1978)
Autolytic risk	Scale for Suicidal Ideation (SSI)	(Beck et al. 1979)
	Hopelessness Scale (HS)	(Beck et al. 1974)
Anxiety	Hamilton Anxiety Rating Scale (HARS)	(Hamilton 1959)
	State Trait Anxiety Inventory (STAI)	(Spielberger et al. 1970)
	Yale-Brown Obsessive Compulsive Scale (Y-BOCS)	(Goodman et al. 1989)
	Clinician Administered PTSD Scale (CAPS)	(Blake et al. 1995)
Psychotic spectrum	Brief Psychiatric Rating Scale (BPRS)	(Overall and Gorham 1962)
	Positive and Negative Syndrome Scale (PANSS)	(Kay et al. 1987)
Personality	International Personality Disorder Examination (IPDE)	(Loranger 1988)
	Eysenck Personality Questionnaire-Revised (EPQ-R)	(Eysenck and Eysenck 1975; Eysenck et al. 1985)
	Millon Clinical Multiaxial Inventory-III (MCMI-III)	(Millon 1983; Millon et al. 2004)
Eating behavior disorders	Eating Disorder Inventory (EDI)	(Garner and Olmsted 1986)
	Eating Disorder Examination (EDE)	(Cooper et al. 1989)
Sexual dysfunction	Changes in Sexual Functioning Questionnaire (CSFQ)	(Clayton et al. 1997)
	Derogatis Interview for Sexual Functioning-Self-Report (DISF-SR)	(Derogatis 1997; Derogatis and Melisaratos 1979)
ADHD	Conners' Adult ADHD Rating Scales	(Conners et al. 1999)
	The World Health Organization Adult ADHD Self-Report Scale (ASRS)	(Kessler et al. 2005)

disability factor, and 6 s-level standardized domains may be obtained: cognition, mobility, self-care, getting along, life activities, and participation.

14.2.4.2 Quality of Life

Quality of Life Enjoyment and Satisfaction Questionnaire

The Q-LES-Q is a self-administered scale of 93 items designed to measure satisfaction and enjoyment in various domains of functioning: physical health and activities, mood state, work, household duties, academic/occupational activities,

Table 14.3 Tests to assess neuropsychological performance

Function	Subcomponent	Instrument	Author
General mental function		Mini Mental State Examination (Mini Mental)	(Folstein et al. 1983)
Attention	**Span and control**	Digit span (WAIS-IV)	(Wechsler 1955, 2008)
		Mental control test	(Wechsler 1955, 2008)
	Sustained or vigilance	Visual Cancellation Test	(Weintraub and Mesulam 1988)
	Selective	Stroop Color and Word Test	(Golden 1976)
	Alternating	Trail Making Test – part B (TMT-B)	(Reitan 1955)
Executive function	**Dysexecutive syndrome**	Behavioral Assessment of the Dysexecutive Syndrome	(Wilson et al. 1996)
	Fluency	Verbal fluency	(Lezak 1995)
	Working memory	Letter-Number (WAIS-IV)	(Wechsler 1955, 2008)
	Flexibility and analogic reasoning	Wisconsin Card Sorting Test (WCST)	(Nelson 1976)
	Interference and inhibitory control	Go/no go task	
	Planning	Key Search and Zoo Map (BADS) plan	(Wilson et al. 1996)
	Decision making	Iowa Gambling Task (IGT)	(Bechara et al. 1994)
Memory	**Broad function**	Wechsler Memory Scale (WMS-III)	(Wechsler 1945, 1998)
	Short-term/working memory	Letter-Number, Arithmetic and Digit Span (WMS-III)	(Wechsler 1945, 1998)
	Episodic long term	Rey Auditory Verbal Learning Test (R-AVLT)	(Rey 1964)
	Semantic long term	Boston Naming Test	(Kaplan et al. 1983)
	Procedural	Rivermead Behavioral Memory Test (RBMT)	(Aldrich and Wilson 1991)
Visuospatial and perceptual abilities		Rey-Osterrieth Complex Figure	(Rey 1942)
Language and communication skills		Information and Comprehension (WAIS-IV)	(Wechsler 1955, 2008)
Premorbid and morbid intelligence		Wechsler Adult Intelligence Scale-IV (WAIS-IV)	(Wechsler 1955, 2008)
		National Adult Reading Test (NART)	(Nelson 1982; Nelson and Willison 1991)

leisure and hobbies, social relationships, and general activities (Endicott et al. 1993). There are various short forms available.

World Health Organization Quality of Life Assessment

The WHOQOL-100 includes 24 facets relating to quality of life, which are grouped into 4 larger domains: physical, psychological, social relationships, and environment (Power et al. 1999). It also includes 1 facet examining overall quality of life

and general health perceptions. There is an abbreviated, self-administered, 26-item version, the WHOQOL-BREF (Skevington et al. 2004), which produces only domain scores.

14.2.4.3 Functioning

Global Assessment of Function

The GAF is a 100-point tool rating overall psychological, social, and occupational functioning of people over 18 years of age and older (American Psychiatric Association 1994, 2013). It excludes physical and environmental impairment. This scale is included in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). However, in DSM-5, the multiaxial system and GAF assessment have been abandoned.

Personal and Social Performance Scale

The PSP is a global measure of personal and social functioning based on four domains of function: self-care, socially useful activities, personal and social relationships, and disturbing and aggressive behavior. Scores may vary from 0 to 100, with a higher score indicating a higher level of social and personal functioning (Morosini et al. 2000).

14.3 Cross-References

- ▶ Drug Testing
- ▶ Medical Disorders and Complications of Alcohol and Other Drugs, Pain and Addiction: An Introduction
- ▶ Motivational Interviewing and Behaviour Change in Addiction Treatment
- ▶ Psychiatric Comorbidities and Complications of Alcohol and Other Drugs: An Introduction
- ▶ Screening, Early Detection and Brief Intervention for Alcohol Use Disorders

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Drug Testing

15

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Contents

Abstract

Drug testing involves the analysis of urine or other body fluids for the presence of prescription drugs, illicit substances, and sometimes other toxins, together

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with their metabolites, for the purpose of diagnosis and monitoring of progress and/or treatment in human subjects. Typically it is employed for clinical, medicolegal, or forensic purposes. This chapter reviews the approach to drug assays that would be undertaken in a hospital biochemistry or toxicology laboratory, where typically a sample of urine has been obtained from the patient. It does not specifically cover "benchtop" or "ward" testing, for which purpose a range of commercial dipstick-type tests have been introduced. The capacity of urine drug screening to determine the recent use of a psychoactive substance is often misunderstood by clinicians, and careful interpretation of the results is needed and should be undertaken in consultation with laboratory staff. The chapter reviews the techniques available for detecting the main classes of drugs including opioids, benzodiazepines, cannabinoids, and psychostimulants.

15.1 Introduction

A range of body fluids or tissues can be assayed for the presence of drugs. No single assay technology or assay strategy will detect all drugs of possible interest.

Comprehensive broad-spectrum analyses for drugs are labor-intensive. For this reason, most clinical laboratories that perform drug testing adopt a limited testing strategy that is designed to satisfy specific clinical needs. If this strategy is to succeed, it is essential that there is good communication between clinicians and laboratorians.

Clinicians should understand the technical limitations of the assay technology used in particular laboratories.

This chapter will discuss the pharmacokinetics of drugs of abuse and what assay technologies are available in the detection of these drugs in body fluids.

A common term used in a request to the laboratory is for a "drug screen." There is no single process that can identify all drugs. Screening processes will attempt to identify commonly abused substances, but many drugs and toxicants are not identified by "screening." Sometimes these drugs/toxicants will not be identified unless there is prior suspicion of their use and "targeted" assays are performed.

Drug screening is done in a number of different contexts. Some of these contexts are listed below:

1. Hospital toxicology
2. Workplace drug testing
3. Forensic toxicology
4. Postmortem toxicology
5. Sports toxicology
6. Drug-facilitated sexual assault
7. Drugs of abuse testing

Hospital toxicology is the investigation of deliberate or accidental overdose of prescription drugs or illicit substances and other toxins, in order to identify the toxicant so that "rational" therapy may be given to the patient. This was the raison

d'être for drug screening when this testing was first introduced into clinical laboratories in the 1970s. Interest in drug screening of this kind has receded over the years, and presently there is an emphasis on supportive therapy while the drug is metabolized and eliminated. The exceptions to this approach are when a specific antidote is available.[1]

Workplace drug testing is done to detect possible impairment of performance of tasks that are performed in the workplace. This testing is of particular importance when the occupation includes operation of dangerous equipment or the operation of vehicles, boats, and aircraft. A special case is the impairment of health-care practitioners who have access to drugs. Addicted individuals use potent synthetic opioids, such as fentanyl. Fentanyl is not detected in conventional screening protocols.

Forensic toxicology is done to provide evidence of a medicolegal nature where poisoning is alleged and may lead in evidence in criminal prosecutions.

Postmortem toxicology is toxicology done to help determine the cause of death.

Sports toxicology is drug testing done to detect the use of performance-enhancing drugs such as anabolic steroids and erythropoietin.

Investigation of drug-facilitated sexual assault involves targeted analysis of some toxicants that are not usually detected in broad-spectrum screening. These drugs include gamma-hydroxybutyrate and ketamine.

Drugs of abuse testing is a term used to indicate testing for the presence of drugs that have a potential for addiction. Sometimes this testing includes assays for drugs used in substitution therapy, such as methadone or buprenorphine, to assess compliance with prescribed therapy.

These different kinds of "drug screening" result in analytical protocols that vary according to the context. Most hospital-based laboratories have protocols that are a combination of "hospital toxicology" and "drugs of abuse testing." Most hospital laboratories do not document chain of custody of sample nor adhere to the rigorous practice demanded for medicolegal testing. Thus, testing that is done for "clinical purposes" does not satisfy the regulatory requirements applied to medicolegal testing.

Drugs of abuse include amphetamine and amphetamine derivatives, benzodiazepines, cocaine, cannabis, and opiates.

The presence of drugs can be determined in a variety of body fluids such as urine, blood, oral fluid, sweat, meconium, and vitreous humor. Drugs can also be detected in hair and body tissues (especially hepatic and renal tissue). All of these matrices offer various advantages and disadvantages.

Urine is the most commonly used matrix for drug detection. Urine samples can be obtained by noninvasive means. Urine offers a longer detection window compared to blood and oral fluid.

[1]Examples are paracetamol and digoxin overdose and methanol or ethylene glycol poisoning. In the case of paracetamol and digoxin toxicity, measurement of the concentration of the drug in serum is more useful than detection in urine.

Urine has the disadvantage that it may be adulterated or substituted at the time of collection. If the testing is to be reliable, the collection should be done under observation. The collection should be done in an area where there are no water sources such as taps and where a dye has been added to cistern water. The temperature of the urine should be tested immediately after collection to determine that the sample has been freshly voided. The creatinine concentration, pH, and the presence of oxidizing agents should also be tested to determine dilution or adulteration that can interfere with testing. Surreptitious adulteration with ammonia solution, bicarbonate, limewater, salt, vinegar, soap, detergents, and bleach can all interfere with immunoassays for drugs of abuse.

15.2 Drug Testing Features

15.2.1 Drug Testing Technologies

Drug testing technology can be classified into two major categories: immunoassay and chromatographic techniques of analysis. The chromatographic techniques of analysis may be further classified into thin-layer chromatography, gas chromatography, and liquid chromatography.

15.2.1.1 Immunoassay

The majority of clinical laboratories use immunoassay on high-capacity automated analyzers as first-line screening. All immunoassays are based on an antibody directed against the drug of interest. Binding of drug in the test sample to the antibody modulates an indicator system. The indicator system produces a signal that is a measure of the amount of drug in the sample. There a number of commercial immunoassays that vary in the indicator system used to indicate drug binding. A further variable is the specificity of the antibody. The cross-reactivity of the antibody to other structurally similar drugs and to drug metabolites is variable for different assay vendors.

The popularity of immunoassays is that most of them can be run on the same analyzers that are used to measure biochemical parameters in a routine biochemistry laboratory. The assays are rapid, do not require sample pretreatment, are supplied as “off-the-shelf” kits, are automated, and use a small volume of raw urine. The assays are validated by the manufacturer.

Four variations of immunoassays are in common use. These assays are:

- Enzyme multiplied immunoassay technique (EMIT, a Siemens trademark)
- Fluorescence polarization immunoassay (FPIA, an Abbott trademark)
- Cloned enzyme donor immunoassay (CEDIA, a Thermo trademark)
- Kinetic interaction of microparticles in solution (KIMS, a technique associated with Roche Abuscreen)

In Australasian laboratories, the CEDIA assays are the most commonly used immunoassays. In the CEDIA assay, ß-galactosidase is present as two inactive enzyme fragments which can reassociate to form the functional enzyme.

One of the inactive fragments is conjugated with drug (this fragment is designated as the "enzyme donor" fragment). If drug is present in the sample, it binds to the drug antibody and the enzyme fragment is free to associate and form the active enzyme. If drug is not present in the sample, the enzyme-drug fragment binds to the antibody and the fragment is not available to form an active enzyme.

Active enzyme cleaves chlorophenol red-ß-D-galactopyranoside to yield free chlorophenol red that can be detected photometrically.

Immunoassays for drugs suffer from the same disadvantages as any immunoassay. False-positive results for particular drugs of abuse can arise because of poor specificity for the drug. One of the popular assay systems uses an antibody to detect amphetamine that cross-reacts with pseudoephedrine.

The antibody used in screening assays for opiate drugs cannot distinguish between the presence of morphine and the presence of codeine. Thus, it is possible to have a positive opiate urine from the ingestion of a popular over-the-counter combination analgesic (paracetamol and codeine).

There is a commercial assay for methadone in urine that is specific for the parent drug and with limited cross-reactivity for the metabolites of methadone (EDDP and EMDP). There is a different assay from the same vendor that is specific for EDDP with low cross-reactivity for the parent drug methadone. This allows detection of a practice in where dispensed methadone was sold to other users. The person on-selling would spike their urine with pharmaceutical methadone to indicate that they had taken methadone and were compliant with the prescribed pharmacotherapy. Testing this urine for the presence of methadone metabolite would yield a negative result and thus rule out that the methadone in the urine resulted from ingestion of the prescribed drug.

Sometimes interpretation of a result depends on knowledge of the antibody specificity and metabolism of the drug.

The initial phase of drug excretion in the urine may have a higher proportion of parent drug than later phases of excretion where drug metabolites may predominate. Different individual may metabolize drug differently to others. Given that antibodies from different manufacturers have different specificities for parent drug and metabolites, any attempt to determine a quantitative result from immunoassay is fraught with difficulty. Further urine can range from dilute to concentrated depending on the state of hydration of individuals.

Clinicians should be aware that immunoassay screening is typically reported as a "negative" or "positive" result. A positive result means that the drug was detected at a concentration that exceeds a threshold concentration (often referred to as a "cutoff" concentration). A negative result does not mean that the drug is absent, rather that the concentration is less than the threshold concentration.

Cutoff concentrations are mandated in a range of jurisdictions, and there is some variability in the concentrations specified. There is an Australian and New Zealand Standard for Drugs of Abuse Testing in urine. The standard is jointly published by Standards Australia and Standards New Zealand and has the formal title of *AS/NZS 4308:2008 Procedures for specimen collection and the detection and quantitation of drugs of abuse in urine*.

This standard mandates the following cutoff concentrations:

- Amphetamine and related compounds, cutoff concentration is 300 μg/L.
- Benzodiazepines, cutoff concentration is 200 μg/L.
- Carboxy-THC (cannabis metabolite), cutoff concentration is 50 μg/L.
- Benzoylecgonine (cocaine metabolite), cutoff concentration is 300 μg/L.
- Morphine and related opiates, cutoff concentration is 300 μg/L.

So what is the rationale for these threshold concentrations? In the United States, there is a federal government-mandated drug testing regime for all federal employees. Regulation in most jurisdictions is based on the template provided by the Substance Abuse and Mental Health Services Administration of the United States (SAMHSA).

The SAMHSA testing has its origins in an Executive Order signed by President Ronald Reagan with the goal of establishing a drug-free federal workplace (Executive Order 12564, signed September 15, 1986). This was prompted by a crash of a military aircraft where drug use was implicated as a cause of the crash.

SAMHSA issues a regulation for testing for the presence of drugs of abuse in body fluids. This regulation is known as "Mandatory Guidelines for Federal Workplace Drug Testing Programs." The first version of the Mandatory Guidelines was promulgated in 1988.

AS/NZS 4308:2008 follows the cutoff concentrations specified by SAMHSA with the exception for amphetamine. For more than 20 years, the SAMHSA-specified cutoff for amphetamine was 1,000 μg/L. This was revised down to 500 μg/L in 2010.

The AS/NZS 4308 standard specifies 300 μg/L as the cutoff concentration for amphetamine, and this is a concentration that might produce a higher rate of false positives. The Preface to AS/NZ 4308:2008 specifically states that the role of the standard is to specify procedures for the testing of specimens "for medical-legal, workplace or court directed testing." The Preface contains an explicit disclaimer that testing for "clinical use or sport" is not covered by the standard. That is, the standard is specifically intended to apply to testing when the results of that testing may be presented in judicial or tribunal proceedings. The AS/NZS 4308 standard prescribes that all urines that test positive in the screening test must be confirmed by chromatographic analysis: thus, a high rate of false positives is of no consequence if there is mandatory confirmation testing.

Many clinical laboratories adopt the cutoff concentrations specified by AS/NZS 4308 even though the testing is performed in a different context to that intended for AS 4308. Clinical laboratories are not required to proceed to confirmatory testing (there are a few clinical laboratories that are accredited to AS 4308, and they would be obliged to perform confirmatory testing).

15.2.2 Chromatographic Techniques for Detecting Drugs of Abuse

Immunoassay depends on the specific of an antibody to bind to a drug molecule. Chromatography takes a different approach: chromatography is a process whereby individual components of a complex mixture are separated and identified.

There are three techniques that can be used to separate and identify drugs in a body fluid such as urine. They are thin-layer chromatography (TLC), gas

chromatography (GC), and liquid chromatography (LC). All of these kinds of chromatography involve a stationary phase and a mobile phase.

In TLC the stationary phase is a thin layer of a sorbent applied to a glass or plastic film as a backing medium or can even be specially formulated paper. The mobile phase is a liquid that migrates up the thin layer by capillary "wicking." The separation is achieved because of differential migration of drugs. Some drugs move rapidly because they have an affinity for the mobile phase, while others move slowly because of an affinity for the stationary phase.

In GC the stationary phase is a polymer that coats the inner wall of a silica capillary tube. The capillary tube is referred to as a column and typically has an internal diameter of 0.25 mm and a length of 30 m. The mobile phase is an inert gas such as helium. As in all forms of chromatography, the separation is achieved by a characteristic distribution of the drug between the stationary phase and the mobile phase. The constraint in gas chromatography is that the compound to be separated must be volatile. Most drugs are not volatile, and this means that they must be converted by chemical reaction into volatile analogues.

In LC the stationary phase consists of small spherical particles of silica. The particles are packed into a stainless steel column (75–150 mm long). In high-performance columns, the beads are 2 μm in diameter. The beads are usually coated with hydrocarbon "whiskers" that are chemically bonded to the underlying silica. The mobile phase is usually water based but with varying amounts of an organic modifier such as methanol or acetonitrile that are used to vary the polarity of the mobile phase. In common with all chromatographic separations, components of a mixture are separated based on their differential distribution between stationary phase and mobile phase.

Prior to performing a chromatographic separation, there is usually some form of sample pretreatment. This pretreatment involves extracting the drug of interest from urine by mixing with a nonmiscible solvent into which the drug is preferentially distributed.[2] This treatment provides a first stage of purification and can be used to concentrate the drug to enhance detection.

Drugs are detected using TLC by direct visualization of a spot after sequentially dipping in or spraying with a range of "visualization" reagents. These visualization reagents react with drugs of interest to give color reactions. Thus, identification of a drug depends on the degree of migration through the stationary phase and the pattern of reaction colors. The advantage of TLC is that it uses simple equipment. The disadvantages of TLC are that it requires extensive training to acquire the pattern recognition skills, it is relatively insensitive, and it does not provide any quantitation of the amount of drug present in the sample.

GC and LC are "instrumental" techniques of analysis, and the equipment is expensive. There are a number of different detectors that can be used to detect the presence of drug that is eluted from the chromatographic column. For drug analysis, the preferred detectors are mass spectrometers (MS).

[2]There is a variation on this procedure that is called solid-phase extraction; this technique will not be discussed here.

Mass spectrometry involves the formation of charged ion(s) from the drug molecule. These charged ions can be sorted in the mass spectrometer and the mass of each ion determined. Hard ionization, such as that produced by subjecting the drug molecule to a beam of electrons, results in extensive fragmentation of the drug molecule. Soft ionization, such that produced using an electrospray ion source,[3] produces limited fragmentation. Different drugs give rise to a distinctive ion "fingerprint."

There is now a trend to the use of "tandem mass spectrometry." In tandem mass spectrometry, one of the ions generated in the ion source is selectively introduced in a collision cell where it collides with inert gas molecules. These collisions induce further fragmentation. The daughter ions produced from the selected precursor ion can be separated and characterized. The two stages of fragmentation of the drug molecule in a tandem mass spectrometer provide greater specificity in the identification of the drug. Thus, drugs are identified based on the time it takes to elute the drug from the chromatographic column (retention time) and the pattern of ions formed after ionization of the drug molecule.

Gas chromatography has the highest resolution of all these modes of chromatography and can typically resolve 100 or more compound in a single chromatographic run. The disadvantage of GC is that it can only be applied to volatile substances so that most drugs have to be derivatized before they can be chromatographed. This is a labor-intensive process.

LC can be used for nonvolatile drugs and does not require chemical derivatization. LC lacks some of the resolving power of GC. Ionization of drugs in the liquid phase results in soft ionization with limited fragmentation, and for this reason tandem mass spectrometry is usually required to give the desired specificity to the analysis. LC-TMS analyzers double the cost of GC-MS analyzers.

15.2.3 Pharmacokinetics and Metabolism

A basic understanding of pharmacokinetics and metabolism is required to estimate windows of opportunity to detect drugs in urine.

15.2.4 Amphetamine

Amphetamine (1-phenylpropan-2-amine) is a molecule consisting of a benzene ring with a 3-carbon side chain; an amino group is substituted on the second carbon of the side chain. The amino group on the side chain confers basic characteristics for this drug, and consequently the rate of renal excretion of the unchanged drug is dependent on urine pH.

[3]Electrospray ionization occurs when solvent is eluted from a chromatographic column and nebulised from a jet, maintained at a high voltage, into a heated gas stream.

Acidic urine inhibits tubular reabsorption and promotes net excretion of amphetamine because the drug is charged at an acidic pH and less likely to diffuse back across the plasma membrane of the tubular epithelium. When the pH of urine is uncontrolled, about 30 % of the drug is excreted unchanged in the first 24 h; if the urine is acidified, this rises to 75 %, and if the urine is alkalinized, the amount excreted unchanged can fall to less than 5 %.

The plasma half-life of amphetamine can vary from 4 h (acidic urine) to 12 h (uncontrolled urinary pH).

The major route of metabolism is oxidative deamination to form phenylacetone which is then hydroxylated to benzoic acid which in turn is converted to hippuric acid. When urine pH is not manipulated, about 50 % of the dose is excreted in the urine as benzoic and hippuric acids.

There are many compounds that are structurally related to amphetamine that have psychoactive properties. These include methamphetamine (crystal meth), methylenedioxyamphetamine (MDA), and methylenedioxymethylamphetamine (MDMA or Ecstasy).

Methamphetamine is the molecule formed when the amino group of amphetamine is substituted with a methyl group to form a secondary amine. MDMA is the molecule formed when there is a methylenedioxy bridge attached to the benzene ring on carbon atoms 3 and 4.

Historically, immunoassays for amphetamines in urine were prone to interference from a range of other drugs including over-the-counter drugs such as pseudoephedrine. The more recent formulations of these kits are less likely to exhibit these cross-reactions. When there is doubt about the veracity of a laboratory result, enquiry should be made of the individual laboratories to determine the performance characteristics of the particular assay that is used.

There is some variation in the performance of immunoassays for amphetamines and related compounds. The most common immunoassay system used in Australia offers two versions of the assay to detect these psychoactive amines. Both versions give 100 % cross-reactivity with amphetamine but have different cross-reactivity for the analogues of amphetamine.

One of the assay systems shows 100 % reactivity for methamphetamine, 2 % reactivity for MDA, and 70 % reactivity for MDMA. The alternate assay system shows 80 % reactivity for methamphetamine, 115 % reactivity for MDA, and 200 % reactivity for MDMA. Assays from other vendors have different patterns of reactivity.

Despite all of these variables, amphetamine and related compounds should be detected in the urine for 48 h after administration of the drug.

15.2.5 Benzodiazepines

Benzodiazepines are drugs that have hypnotic, anxiolytic, and anticonvulsant activity. There are many compounds fall within this class of drugs. They vary in their patterns of metabolism and their spectrum of physiological effects. The pharmacology of benzodiazepines is complex because many of the metabolites of the parent drugs are biologically active themselves.

The variety of chemical structures that possess these properties is extensive. This chapter will restrict discussion to the 12 compounds of this class that are used clinically in Australia. They are shown in Table 15.1.

The chemical structures of these compounds are shown in Fig. 15.1.

All of these compounds include a benzene ring fused with a diazepine ring. A diazepine ring is a 7-member heterocyclic compound that contains two nitrogen atoms. The atoms of the diazepine ring are numbered 1–5 starting with the nitrogen atom closest to the benzene ring (atoms involved in the fusion of the two rings are not counted).

In all of these compounds, the nitrogen atoms are located at positions 1 and 4 (called a 1, 4-benzodiazepine). The exception is clobazam where the nitrogen atoms are in positions 1 and 5 (a 1, 5-benzodiazepine).

With the exception of bromazepam, all of these benzodiazepines have an aryl substituent attached to position 5 in the diazepine ring. Bromazepam is substituted at position 5 with a pyridine ring.

Midazolam includes a fused diazolo ring. A diazolo ring is a five-member heterocyclic ring that includes two nitrogen atoms.

Alprazolam and triazolam include a fused triazolo ring. A triazolo ring is a five-member heterocyclic ring that includes three nitrogen atoms.

All of these benzodiazepines include substitution of a carbon atom in the fused benzene ring. This carbon atom is the para position relative to the carbon closest to the nitrogen in the diazepine ring. This position is sometimes numbered as carbon 7, sometimes as carbon 8, and sometimes as carbon 9.

This carbon is variously numbered because of the convention in numbering atoms in fused ring systems.

In six of the benzodiazepines, this "para" carbon atom is numbered as atom 7 (bromazepam, clobazam, clonazepam, diazepam, oxazepam, and temazepam).

In three of the benzodiazepines, this carbon atom is numbered as atom 8 (alprazolam, midazolam, and triazolam).

Table 15.1

Benzodiazepine	Duration of action[4]
Alprazolam	Intermediate acting
Bromazepam	Intermediate acting
Clobazam	Long acting
Clonazepam	Long acting
Diazepam	Long acting
Flunitrazepam	Long acting
Lorazepam	Intermediate acting
Midazolam	Short acting
Nitrazepam	Long acting
Oxazepam	Intermediate acting
Temazepam	Intermediate acting
Triazolam	Short acting

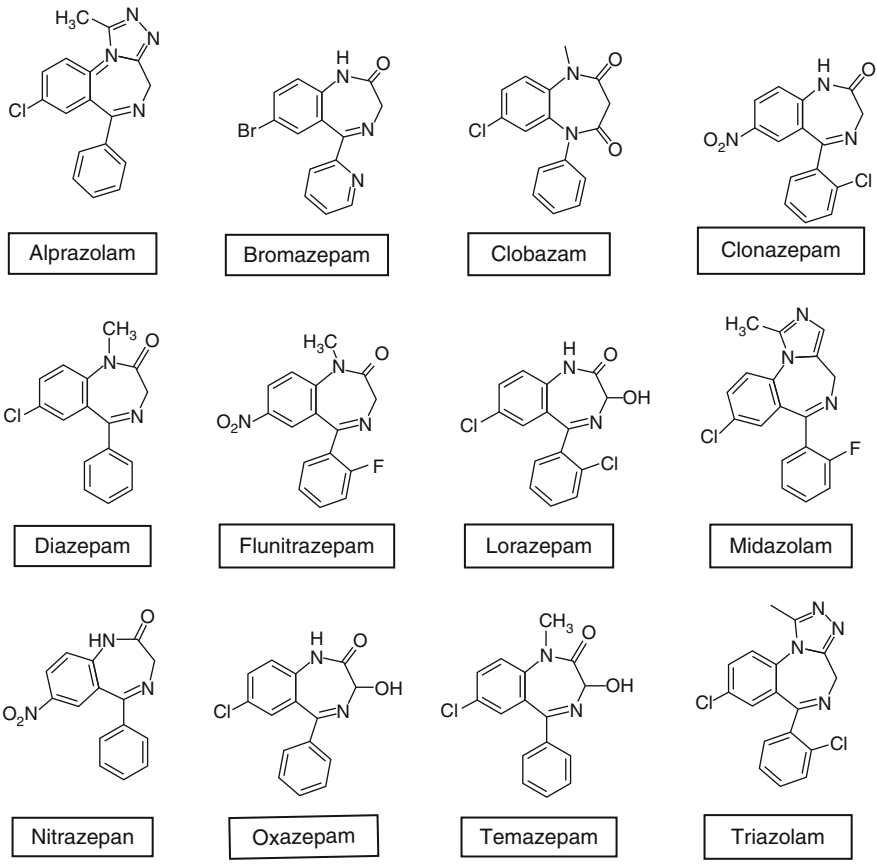


Fig. 15.1

In three of the benzodiazepines, this carbon atom is numbered as atom 9 (flunitrazepam, lorazepam, and nitrazepam).

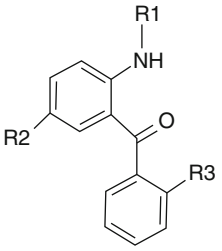
Eight of the twelve benzodiazepines have a chlorine substituent in the para position. Bromazepam is substituted with a bromine atom in this position. Clonazepam, flunitrazepam, and nitrazepam are substituted with a nitro group in the para position.

15.2.6 Metabolism

The metabolism of the benzodiazepines involves three main reactions:

- Hydroxylation at carbon 3 of the diazepine ring
- Dealkylation of the 2-methyl group of diazepam, flunitrazepam, midazolam, and temazepam

- Dealkylation of the methyl substituent of the diazolo ring of midazolam
- Dealkylation of the methyl substituent of the triazolo ring of alprazolam
- Hydroxylation of the methyl substituent of the diazolo or triazolo benzodiazepines
- Reduction of the nitro group of clonazepam, flunitrazepam, and nitrazepam to form amino metabolites of these benzodiazepines
- Hydrolytic cleavage of the diazepine ring to form an amino-benzophenone with the elimination of glycine



Aminobenzophenone

There is extensive glucuronidation all of these metabolites.

There is minimal or no excretion of the unconjugated parent drug. Most of the benzodiazepines undergo significant metabolism. The exceptions are oxazepam, temazepam, and lorazepam that are excreted largely as the glucuronide.

15.2.7 Alprazolam

The two major metabolites are α-hydroxyalprazolam (where the methyl substituent of the triazolo ring is hydroxylated) and 4-hydroxyalprazolam where carbon 4 of the diazepine ring is hydroxylated. Both metabolites are active. The α-hydroxyalprazolam represents 15 % of the dose of the parent drug and the 4-hydroxyalprazolam represents about 60 % of the dose. The remainder is made up of minor metabolites such as the benzophenone derivative and desmethylalprazolam.

15.2.8 Bromazepam

The two major metabolites are 3-hydroxybromazepam (30 %) and the benzophenone derivative (40 %). These two metabolites are extensively conjugated.

15.2.9 Clobazam

Clobazam is highly lipophilic and is metabolized slowly: about 90 % of a dose is excreted in the urine in 17 days. It is metabolized by demethylation and

hydroxylation. The metabolites are desmethylclobazam (an active metabolite) and 4-hydroxyclobazam and 4-hydroxydesmethylclobazam.

15.2.10 Clonazepam

The major metabolic reaction is reduction of the nitro group to 7-aminoclonazepam, followed by acetylation to 7-acetamidoclonazepam. Hydroxylation of clonazepam and its 2 metabolites also occurs. All metabolites are extensively conjugated. 70 % of the dose is excreted as 7-aminoclonazepam and 7-acetamidoclonazepam.

15.2.11 Diazepam

The major routes of metabolism are demethylation to form desmethyldiazepam and 3-hydroxylation. Desmethyldiazepam (nordiazepam) is an active metabolite that accumulates during chronic dosing. Desmethyldiazepam can be further metabolized to form oxazepam (an active metabolite). Diazepam can also be hydroxylated to form temazepam, another active metabolite. There is considerable interperson variation in the proportion of the metabolites formed although oxazepam is the major metabolite and is excreted as the glucuronide.

15.2.12 Flunitrazepam

Flunitrazepam is extensively metabolized to desmethylflunitrazepam and 7-aminoflunitrazepam. Other metabolites include 3-hydroxyflunitrazepam, 3-hydroxy-7-acetamidoflunitrazepam, and 7-amino-1-desmethylflunitrazepam.

15.2.13 Lorazepam

Lorazepam is excreted in the urine as the inactive glucuronide. There is no other metabolism of any significance.

15.2.14 Midazolam

Midazolam is metabolized by hydroxylation to 1-hydroxymethylmidazolam and 4-hydroxymidazolam. These hydroxy metabolites are then conjugated with glucuronic acid and cleared rapidly (90 % of a dose is excreted in the urine in 24 h).

15.2.15 Nitrazepam

Nitrazepam is metabolized to 7-aminonitrazepam and then to the 7-acetamido derivative. There is some formation of 3-hydroxy derivatives of these metabolites.

There is also cleavage of the diazepine ring to yield 2-amino-5-nitrobenzophenone and 2-amino-3-hydroxy-5-nitrobenzophenone. All the metabolites are inactive.

15.2.16 Oxazepam

Oxazepam is glucuronidated and excreted in the urine. Only traces of unchanged oxazepam and other minor metabolites can be detected in the urine. Oxazepam is a metabolite of diazepam and temazepam.

15.2.17 Temazepam

Temazepam is largely excreted as the glucuronide. There is limited demethylation to form oxazepam. Temazepam is a metabolite of diazepam.

15.2.18 Triazolam

The major metabolite of triazolam is 1-hydroxymethyltriazolam which has similar activity to the parent drug. Minor metabolites are 4-hydroxytriazolam, 1-hydroxymethyl-4-hydroxytriazolam, and dichlorotriazolylbenzophenone derivatives.

15.2.19 Immunoassay Detection of Benzodiazepines

Table 15.2 shows the specificity of a commonly used immunoassay for benzodiazepines.

The assay has probably been standardized to nitrazepam because this drug shows 1,005 cross-reactivity. Diazepam shows 247 % cross-reactivity, and clobazam shows 62 % cross-reactivity. The glucuronides of temazepam, oxazepam, and lorazepam exhibited minimal reaction in the assay system unless the urine was treated with ß-glucuronidase to hydrolyze the conjugate and release free drug or metabolite. Glucuronidation is the major route of biotransformation of these 3 benzodiazepines so treatment with ß-glucuronidase is essential to detect these drugs.

15.2.20 Cannabinoids

The hemp plant C*annabis sativa* synthesizes a psychoactive compound called tetrahydrocannabinol. Tetrahydrocannabinol is the main psychoactive compound found in the plant, but it is one of over 60 closely related compounds that are collectively referred to as cannabinoids.

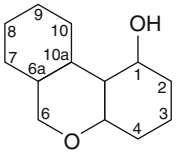
Table 15.2 Specificity of the CEDIA® Benzodiazepine Assay for various benzodiazepines and their metabolites[a]

Drug/metabolite	Percent cross-reactivity without ß-glucuronidase treatment	Percent cross-reactivity with ß-glucuronidase treatment
7-aminoflunitrazepam	Not tested	99
7-aminonitrazepam	Not tested	83
α-Hydroxyalprazolam	188	167
α-Hydroxytriazolam	193	155
Alprazolam	205	220
Alprazolam glucuronide	Not tested	100
Bromazepam	110	104
Clobazam	62	59
Clonazepam	140	71
Desalkylflurazepam	210	173
Diazepam	247	154
Flunitrazepam	135	109
Lorazepam	122	115
Lorazepam glucuronide	1	45
Aminoclonazepam	Not tested	96
Nitrazepam	100	100
Desmethyldiazepam	211	173
Oxazepam	107	125
Oxazepam glucuronide	1	25
Temazepam	144	93
Temazepam glucuronide	1	25
Triazolam	191	217

[a]Adapted from the Thermo Scientific Benzodiazepine Assay Package Insert dated November 2002

It is difficult to follow the metabolism of tetrahydrocannabinol without a basic understanding of the structure of the molecule. Tetrahydrocannabinol is the derivative of a fused ring system named tetrahydrobenzo[c]chromen-1-ol. The chromen-1-ol part of the name refers to a benzene ring fused to a furan (a 6-membered heterocyclic ring containing an oxygen atom), and the benzene ring is substituted with a hydroxyl group at carbon number 1. The tetrahydrobenzo group is the third ring structure fused to the chromen-1-ol system; the tetrahydrobenzo ring is a 6-membered carbon ring that is not an aromatic ring (it has four extra hydrogen atoms attached to the ring carbons that prevent the ring from displaying aromatic character).

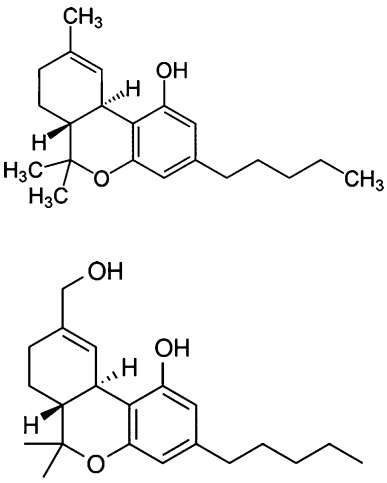
The numbering convention is shown below:



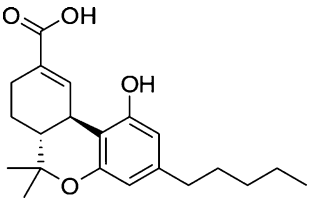
Tetrahydrocannabinol has the structure shown below.

The formal chemical name of tetrahydrocannabinol (THC) is 6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-ol. There are 2 methyl substituents on the benzene ring at ring position 6 and a further methyl group attached at position 9. There is a pentyl substituent on carbon number 3. The nonaromatic ring has 2 hydrogen atoms bonded to carbon atom numbers 6a, 7, 8, and 10a.

The first step in the metabolism of tetrahydrocannabinol is the hydroxylation of the methyl group attached to the carbon in position 9 of the ring system. The formal name of this metabolite is 9-(hydroxymethyl)-6,6-dimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-ol. Simpler nomenclature calls this compound 11-hydroxy-tetrahydrocannabinol or 11-OH-THC; the structure is shown below.



11-Hydroxy-tetrahydrocannabinol is known to be psychoactive but has a limited role in the pharmacology of cannabis. Hydroxy-THC is rapidly metabolized to form a carboxylated metabolite. The carboxylated metabolite has the formal name 1-hydroxy-6,6-dimethyl-3-pentyl-6a,7,8,10a-tetrahydrobenzo [c]chromene-9-carboxylic acid, but this name is conveniently shortened to 11-*nor*-9-carboxy-delta-9-tetrahydrocannabinol or simply carboxy-THC. The structure is shown below:



Carboxy-THC is not psychoactive and is extensively conjugated with glucuronic acid before excretion into urine. The cutoff concentration for immunoassay of "cannabis metabolites" is set at 50 μg/L in the Australasian Standard AS/NZS 43008. This standard prescribes a negative report if the immunoassay screening is less than the cutoff concentration and confirmatory testing does not proceed. If a positive result is obtained in the immunoassay screen, it is then mandatory to confirm by chromatographic testing, and the confirmatory cutoff concentration nominated by the standard specifically for carboxy-THC is 15 μg/L. Hydrolysis of the glucuronide of carboxy-THC is rarely performed prior to immunoassay but is mandatory before confirmatory chromatographic analysis. One of the commonly used immunoassays is calibrated with carboxy-THC (i.e., carboxy-THC shows 100 % cross-reactivity); the assay shows a 63 % cross-reactivity to the glucuronide of carboxy-THC. By way of contrast, the parent psychoactive compound THC shows a 28 % cross-reactivity and hydroxy-THC shows a 42 % cross-reactivity.

The specified cutoff concentrations are a compromise: if the cutoff is set too low, it could produce a "positive" result from passive smoking. If the cutoff is set too high, then true positives might not be detected. The effect of passive smoking has been the subject of a number of studies, and the consensus is that passive smoking is unlikely to result in a urinary concentration of cannabis metabolites that exceeds 50 μg/L.

The half-life for elimination of carboxy-THC is about six days. The precursor compound THC is lipophilic and has a high volume of distribution of about 10 L per kilogram of bodyweight. Chronic users of cannabis establish a significant reservoir of carboxy-THC in the adipose tissue. During periods of abstinence, THC is slowly released into the systemic circulation and metabolized to hydroxy-THC and carboxy-THC: about 70 % of these metabolites are excreted in the feces and about 30 % is eliminated in the urine. The time taken for carboxy-THC to fall below the cutoff concentrations of the metabolite in the urine is therefore dependent on the amount of THC stored in tissue lipids.

Following a single occasion of cannabis use, the urinary concentration of carboxy-THC, determined by GC-MS, falls below a cutoff concentration of 50 μg/L within 72 h. Moderate users of cannabis (defined as four occasions per week) typically fall to the cutoff concentration within 5–7 days after ceasing use of the drug. Daily use of cannabis typically exhibits a fall to the cutoff concentration within 12 days of ceasing use. Carboxy-THC may be detected in the urine of chronic heavy users for greater than 30 days after cessation of use.

Given the extended period of detection of carboxy-THC in the urine of long-term heavy users of the drug, the question is often posed if there is continued use. This may be a pertinent question in persons on drug rehabilitation programs, which require abstinence, or when use is proscribed by judicial proceedings. One approach to this issue is to determine a carboxy-THC to creatinine ratio for urine samples collected at different times. A comparison of these two ratios and consideration of the time elapsed between the two samples taken allow an assessment of continued use. The stringency of the criteria that are applied in comparing these ratios influences the

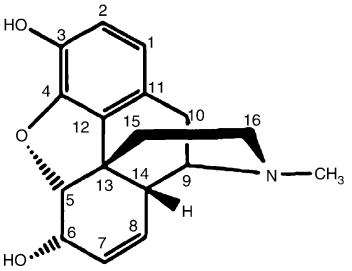
reliability of the assessment. Stringent criteria will give a high probability of a true positive result, whereas less stringent criteria may detect more recidivist behavior but at the risk of false-positive results (Identifying New Cannabis Use with Urine Creatinine-Normalized THCCOOH Concentrations and Time Intervals between Specimen Collections, M. L. Smith, A. J. Barnes, and M. A. Huestis, Journal of Analytical Toxicology, volume 33, May 2009, page 185). Clinicians should contact their local provider of laboratory testing to determine an appropriate testing strategy for the care of their patients.

15.2.21 Opiates and Opioids

Opium is the dried sap that is exuded when the seedpods of the opium poppy (*Papaver somniferum*) are scored. Crude opium contains about 25 alkaloids. Alkaloids are plant products that are bases because they contain a heterocyclic ring that includes a nitrogen atom. Many alkaloids have pharmacological activity. The main alkaloids in opium are morphine, codeine, and thebaine.

Morphine can be isolated in pure form from opium. Both licit and illicit sources of morphine are derived from the cultivation of poppies. The term opiates is used to describe drug substances that are purified from opium or are simple derivatives of the opium alkaloids: this includes morphine, codeine, and heroin. The term opioids includes all substances that have a morphine-like activity whether they are naturally occurring alkaloids, semisynthetic drugs such as hydrocodone and hydromorphone, or synthetic drugs that include buprenorphine, fentanyl, methadone, and oxycodone.

The morphine molecule consists of five fused rings. There is a benzene ring fused to a cyclohexane ring (6 carbon unsaturated ring) which in turn is fused to a cyclohexene ring (6 carbon unsaturated ring). The benzene ring and the cyclohexene ring are joined by a tetrahydrofuran ring (5 atom ring containing an oxygen atom). These four fused rings form a rigid structure in one plane; above this plane is a piperidine ring (6-membered ring containing a nitrogen atom). Piperidine shares carbon atoms with the four ring systems at positions 9, 13, and 14 (see the structure below).



Morphine has two hydroxyl groups, one at position 3 and one at position 6. These two hydroxyl groups can react with acetic acid (or acetic anhydride) so that two acetyl groups are added to the molecule via an ester link. The resulting

molecule is 3,6-diacetylmorphine (diamorphine or heroin). Codeine has the same structure as morphine excepting the 3-hydroxyl group is replaced by a methoxy (CH_3O–) group.

Heroin is rapidly metabolized to both 3-monoacetylmorphine and 6-monoacetylmorphine. The half-life of heroin in the systemic circulation is about 3 min.

The 3-monoacetylmorphine is inactive because it lacks a free hydroxy group at position 3 that is essential for receptor binding; 6-monoacetyl has double the potency of morphine but it too is rapidly deacetylated to morphine with a half-life of about 5 min.

Diamorphine and 6-monoacetylmorphine both are more lipophilic than morphine and cross the blood-brain barrier more easily than morphine. Diamorphine can be detected in CSF within 15–20 s of intravenous administration.

After parenteral administration of morphine, 90 % of the drug is excreted in the urine in the following 24 h. Morphine is mainly excreted as the 3-glucuronide and the 6-glucuronide. The plasma half-life is about 3 h.

Intact codeine has minimal analgesic activity; the analgesic effect exerted by codeine only occurs after the drug has been O-demethylated to yield morphine. The demethylation occurs mainly in the liver due to the action of the CYP2D6 cytochrome (this is a polymorphic enzyme with significant interindividual variation in the rate of demethylation). Following oral administration, about 60 % of the dose is excreted as free or conjugated codeine, and about 20 % is excreted as free or conjugated morphine. The plasma half-life of codeine is about two hours.

There are several issues with the interpretation of immunoassays of urine that are positive for opiates. Most immunoassays do not distinguish between codeine and morphine. Codeine is present in some over-the-counter analgesic, whereas morphine is subject to more intense regulation (regulated as a Schedule 8 Controlled Drug in Australia) or morphine may be present in urine because of the illicit use of heroin.

Standard AS/NZS 4308 prescribes a cutoff of 300 μg/L for immunoassay screening for the presence of an opiate in urine. Most Australian clinical laboratories, whether accredited to the standard or not, continue to report a positive opiate when this cutoff is exceeded. This 300 μg/L cutoff was originally specified by SAMHSA but was increased to 2,000 μg/L in 1998 because the threshold as originally set could be exceeded by ingestion of poppy seed legitimately used in food products.

Urines that test positive to an immunoassay for opiates can be tested using chromatographic techniques where it is easy to quantify individual opiates. When these data are available, some rules can be applied to contribute the source of the opiate:

- If the total codeine concentration in the urine sample is >300 μg/L and the ratio of the morphine concentration to the codeine concentration >2, then it is probable that these opiates occur in the urine because of ingestion of codeine alone.

- If the total morphine concentration in the urine sample is greater than 1,000 μg/L and the ratio of the morphine concentration to the codeine concentration is $1 < 2$, then poppy seeds can be excluded as the sole source for the positive opiate test result.
- If the total morphine concentration in the urine sample is greater than 1,000 μg per ml and no codeine is detected, then it is likely that the positive opiate result is due to the use of morphine or heroin (The Clinical Toxicology Laboratory, Page 87, AACC Press, 2001).

Table 15.3 shows the cross-reactivity of a commercial reagent system for detection of opiates (Cedia Opiates, Thermo Scientific).

The assay is calibrated to morphine, and codeine shows 125 % cross-reactivity, whereas diacetylmorphine and other morphine metabolites show a cross-reactivity between 48 % and 57 % (Table 15.3). It should be noted that some semisynthetic opiate agonists such as pethidine, oxymorphone, and oxycodone show minimal activity in the immunoassay system, whereas other semisynthetic agonists show 50–57 % cross-reactivity.

Thus, a "negative" screen for "opiates" does not exclude abuse of a number of opiates and opioids. If this is an issue of concern, practitioners should enquire of their service provider to determine the specificity of the immunoassay used.

It should be noted that a number of assay vendors offer immunoassays that are directed at a particular opiate or opioid and are relatively specific for the compound of interest. These assays may not be offered by hospital biochemistry laboratories on a routine basis. The sample may need to be forwarded to a specialist drug assay laboratory. Such opioids include buprenorphine, pethidine, oxycodone, tramadol, and methadone.

The general rule is that opiates that react in screening assay can be detected for 2 days after a single occasion of use.

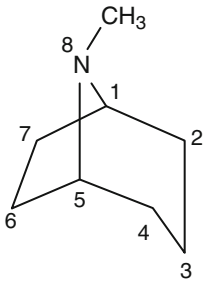
Table 15.3

Drug/metabolite	Cross-reactivity
Morphine	100
Codeine	125
Diacetylmorphine	53
Dihydrocodeine	50
Hydrocodone	48
Hydromorphone	57
Morphine-3-glucuronide	81
Morphine-6-glucuronide	47
6-Monoacetylmorphine	81
Pethidine (meperidine)	0
Oxymorphone	2
Oxycodone	3

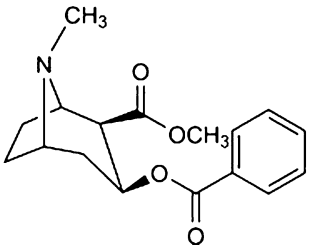
Fentanyl deserves special comment: it is a very potent opioid which means concentrations of the drug in the urine are quite low following licit or illicit use. Detection requires sophisticated technique and sensitive analyzers that will not be available in many laboratories. These technical challenges are known to health professionals who have access to this drug, and fentanyl may become their drug of choice if inclined to drug abuse. There has been a substantial increase in the use of sustained-release transcutaneous patches of fentanyl in treatment of chronic pain or in a palliative care context. It is a relatively simple matter to extract the drug from these patches for intravenous injection and there evidence of a black market for these patches in some jurisdictions.

15.2.22 Cocaine

Cocaine, scopolamine, hyoscyamine, and atropine are examples of tropane alkaloids that occur in the plants. Two families of plants contain tropane alkaloids: Erythroxylaceae (coca) and Solanaceae. These compounds contain a bicyclic 8-membered ring with a nitrogen bridge joining carbon atom 1 and carbon atom 5.



Cocaine has a methyl ester attached at carbon 2 of the tropane ring and a benzoyl ester attached to carbon 3. A trivial name for cocaine is methylbenzoylecgonine.

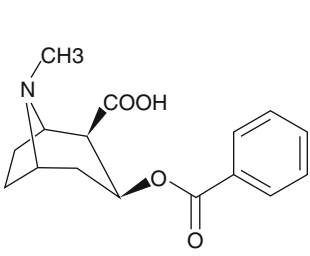


The metabolism of cocaine involves hydrolysis of the two ester bonds in the drug. The major metabolite is benzoylecgonine formed when the methyl ester is hydrolyzed to yield a carboxyl on carbon 2 of the tropane ring. About 45 % of the dose is excreted in the urine as benzoylecgonine.

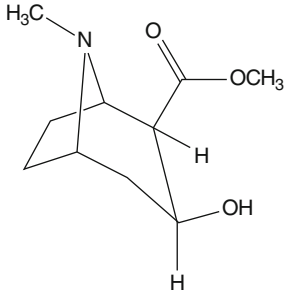
Table 15.4

Drug/metabolite	Cross-reactivity
Benzoylecgonine	100
Cocaine	54
Ecgonine	1
Methylecgonine	0

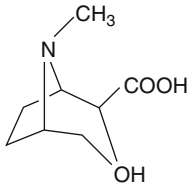
Methyl ecgonine is formed when the benzoyl ester is hydrolyzed to yield an hydroxyl group on carbon 3 of the tropane ring. About 40 % of the dose is excreted in the urine as methyl ecgonine. Both ester links of cocaine may be hydrolyzed to yield ecgonine which is a minor metabolite of cocaine. Only a small proportion of the dose, about 55 %, is excreted as the parent drug.



Benzoylecgonine



Methylecgonine



Ecgonine

Table 15.4 shows the specificity of a commonly used immunoassay for cocaine. The assay is calibrated to the major metabolite, benzoylecgonine. There is limited reaction to cocaine (54 %) and virtually no reaction to the minor metabolites of cocaine.

The cutoff concentration for immunoassay screening is specified as 300 μg/L of "cocaine metabolite"; given the specificity of most assays and the pattern of urinary excretion of metabolites, this equates to a concentration of 300 μg/L of benzoylecgonine.

The standard specifies a lower cutoff concentration for chromatographic confirmatory assays. The confirmatory test is reported as positive if benzoylecgonine is detected at a concentration $\geq$150 μg/L or if methylecgonine is detected at a concentration $\geq$150 μg/L.

Benzoylecgonine can be detected in the urine after a single occasion of use for about 72 h.

Biological State Marker for Alcohol Consumption

16

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Abstract

Alcohol-related disorders are common, expensive in their entire course, and often underdiagnosed. To facilitate early diagnosis and therapy of alcohol-related disorders and thus prevent later complications, questionnaires and biomarkers are useful. Indirect state markers like gamma-glutamyl transpeptidase (GGT), mean corpuscular volume (MCV), and carbohydrate deficiency transferrin (CDT) are influenced by age, gender, various substances, and non-alcohol-related illnesses and do not cover the entire timeline for alcohol consumption. Direct state markers as ethyl glucuronide (EtG), phosphatidylethanol (PEth), and fatty acid ethyl esters (FAEEs) have gained enormous interest in the last decades as they are metabolites of alcohol becoming only positive in the presence of alcohol. As biomarkers with high sensitivity and specificity covering the complimentary timeline, they are already routinely in use and contribute to new perspectives in prevention, interdisciplinary cooperation, diagnosis, and therapy of alcohol-related disorders.

16.1 Introduction

Alcohol-related disorders are in the top ten of the most common diseases worldwide (World Health Organization (WHO) 2011). The point prevalence for alcohol dependence in Germany, as in other comparable countries, is 5 % and the lifetime prevalence is 10 % (Mann 2002). Worldwide, approximately 4 % of deaths are attributable to alcohol, greater than deaths caused by HIV, violence, or tuberculosis (World Health Organization (WHO) 2011). The yearly costs attributable to alcohol in Europe are approximately 270 billion € and in Germany 26.7 billion € (DHS). The costs include medical care; decreased productivity caused by illness, accidents, and death; and the social burden, e.g., in the family (World Health Organization (WHO) 2011).

In general hospitals, a rate of up to 20 % of all inpatients having an alcohol use disorder was found; in surgical departments rates from 16 % to 35 % in patients with multiple trauma were described (Tonnesen and Kehlet 1999; Spies et al. 2001). These patients have a prolonged hospital stay (Tonnesen and Kehlet 1999; Spies et al. 2001; Rubinsky et al. 2012); they have to be treated 1.5 days longer in ICUs

(Rubinsky et al. 2012) and are twice likely to return to OR due to complications (Rubinsky et al. 2012). The post-traumatic lethality is up to four times higher in individuals with alcohol use disorders (Tonnesen and Kehlet 1999; Spies et al. 2001). Of all alcohol-dependent individuals, 80 % are treated by general practitioners and only 34 % in general hospitals (Mann 2002). Thus, alcohol-related disorders are common, expensive in their entire course (Rehm et al. 2009), and often underdiagnosed (Moore et al. 1989).

To facilitate early diagnosis and therapy of alcohol-related disorders and thus prevent later complications, questionnaires like the CAGE questionnaire (Ewing 1984) or the Alcohol Use Disorders Identification Test (AUDIT) (Saunders et al. 1993) and biomarkers are useful.

Indirect state markers as well as direct state markers are routinely used to detect alcohol. The indirect state markers like gamma-glutamyl transpeptidase (GGT), mean corpuscular volume (MCV), and carbohydrate deficiency transferrin (CDT) are influenced by age, gender, various substances, and non-alcohol-related illnesses and do not cover the entire timeline for alcohol consumption (Conigrave et al. 2002; Laposata 1999; Helander 2003a; Hannuksela et al. 2007; Niemelä 2007; Allen et al. 2009).

Direct state markers have gained enormous interest in the last decades as they are metabolites of alcohol becoming only positive in the presence of alcohol. As biomarkers with high sensitivity and specificity covering the complimentary timeline, they are already routinely in use and contribute to new perspectives in prevention, interdisciplinary cooperation, diagnosis, and therapy of alcohol-related disorders.

16.2 Direct Ethanol Metabolites

Routinely used direct ethanol metabolites are:

- Ethyl glucuronide (EtG), in serum, urine, and hair (Alt et al. 2000; Dahl et al. 2002, 2011a; Schmitt et al. 1995; Skipper et al. 2004a; Schlögel et al. 2005; Wurst et al. 1999a, b; Wurst and Metzger 2002; Wurst et al. 2003a, b, 2004a, 2008a, b, c, d, 2011; Politi et al. 2006; Junghanns et al. 2009; Halter et al. 2008; Wiens et al. 2008; Albermann et al. 2012a; Ferreira et al. 2012; Hoiseth et al. 2012, 2013; Hagström et al. 2012; McDonell et al. 2012; Stewart et al. 2013; Redondo et al. 2012)
- Ethyl sulfate (EtS), in urine and serum (Dresen et al. 2004; Helander and Beck 2004; Wurst et al. 2006)
- Phosphatidylethanol (PEth) in whole blood (Alling et al. 1983; Aradottir et al. 2006; Varga et al. 1998; Hartmann et al. 2007; Marques et al. 2010, 2011; Kip et al. 2008; Gnann et al. 2009, 2012; Zheng et al. 2011; Nissinen et al. 2012; Isaksson et al. 2011; Wurst et al. 2010; Wurst and Thon 2012; Loftus et al. 2011; Stewart et al. 2009, 2010; Faller et al. 2011)

- Fatty acid ethyl ester (FAEEs) especially in hair (Auwärter et al. 2001; Pragst et al. 2001; Appenzeller et al. 2007a; Pragst and Yegles 2007)

Direct ethanol metabolites are detectable in serum for hours, in urine for up to 7 days, in whole blood over 2 weeks, and in hair over months.

16.2.1 Ethyl Glucuronide

Ethyl glucuronide (EtG) is a phase II metabolite of ethanol and has a molecular weight of 222 g/mol. It is metabolized by the UDP-glucuronosyltransferase (Foti and Fisher 2005).

It is not relevant for the alcohol elimination (less than 0.1 %), but it can function as a biomarker as it is only detectable in the presence of ethanol. EtG is nonvolatile, water soluble, and stable in storage and can, depending on the amount consumed and time spent for consumption, still be detectable in the body long after completion of alcohol elimination (Wurst et al. 2004a; Borucki et al. 2005). According to Walsham and Sherwood (2012), EtG can be detected of up to 90 h in urine. There is no difference regarding the elimination rate between a healthy population and heavy alcohol consumers at the beginning of detoxification treatment (Høiseth et al. 2009).

Ethyl glucuronide can also be detected in postmortem body fluids and tissues like gluteal and abdominal fat, liver, brain, and cerebrospinal liquor (Wurst et al. 1999b), even in bone marrow and muscle tissue (Schlögel et al. 2005).

Even small amounts like 0.1 l champagne can be detected up to 27 h. Experiments with 1 g ethanol (champagne, whisky) (Thierauf et al. 2009a) as well as use of mouthwash (Costantino et al. 2006) and hand sanitizer gels (Rohrig et al. 2006) yielded ethyl glucuronide concentrations of less than 1 mg/L in urine. Measurable concentrations in urine were found up to 11 h. This aspect is of relevance regarding unintentional exposure of alcohol. Pralines, nonalcoholic beer, pharmaceutical products, fruit juice, sauerkraut, mouthwash products, and hand sanitizer gels may contain small amounts of alcohol. Even the intake of 21–42 g yeast with approximately 50 g sugar leads to measureable EtG and EtS concentrations in urine (Thierauf et al. 2010).

Therefore, a patients' claim not having consumed alcohol may be the truth even when EtG is detectable in urine. Since patients in withdrawal treatment should avoid even the smallest amount of alcohol, they have to be informed of such hidden sources of ethanol to avoid unintentional alcohol intake. A differential cutoff of 0.1 mg/L in cases where total abstinence is the goal, and 1.0 mg/L if small amounts of alcohol intake are tolerated, has been recommended for practical reasons (Costantino et al. 2006).

Selected applications for the use of EtG:

1. Specific high-risk group:

Many patients in opioid-maintenance therapy suffer from hepatitis C (HCV) infection. Alcohol consumption, especially in large amounts, leads to the progression of cirrhosis (Gitto et al. 2009; Safdar and Schiff 2004). One study in Sydney (Wurst et al. 2008d) and one in Basel (Wurst et al. 2011) showed the usefulness

and necessity of the determination of ethyl glucuronide in patients in opioid-maintenance therapy. In the former study, of all EtG-positive patients, 42 % (n = 8 of 19) would have not reported the alcohol consumption (Wurst et al. 2011). In the latter one, 75 % consumed alcohol according to the hair analysis for EtG; however, two thirds did not report about it (Wurst et al. 2011).

The use of direct ethanol metabolites in high-risk groups therefore allows more possibilities for therapeutic interventions, consequently leading to improvement in the quality of life.

2. Monitoring programs:

One example for using ethyl glucuronide successfully in monitoring programs are the Physician Health Programs in the USA which provide a nondisciplinary therapeutic program for physicians with potentially impairing health conditions as, for example, substance-related disorders. Being in the monitoring program, physicians with substance-related disorders are allowed to keep on working, whereas a regularly proof of abstinence has to be shown. Measuring EtG in urine, Skipper and colleagues (Skipper et al. 2004b) showed that of 100 random samples collected, no sample was positive for alcohol using standard testing; however, seven were positive for EtG (0.5–196 mg/l), suggesting recent alcohol use. EtG testing can provide additional information and, consequently, may lead to further treatment and improvement for the patient (Skipper et al. 2004b).

3. Pharmacotherapeutic studies:

As an objective outcome parameter, EtG testing has shown to be useful in pharmacotherapeutic studies (Dahl et al. 2011b; Mitchell et al. 2012).

4. Liver transplantation:

Liver transplantations are in 20–30 % related to alcohol (Burroughs et al. 2006). Postoperatively, 20–25 % of the patients lapse or relapse to alcohol intake (Kelly et al. 2006; DiMartini et al. 2006). In 18 patients with ALD (alcohol liver disease), Erim et al. (2007) found no self-report on alcohol consumption. One out of 127 tests for breath alcohol was positive, whereas 24 of 49 urine samples were positive for EtG. Comparable results were reported by Webzell et al. (2011) who found self-reported alcohol consumption in 3 % in contrast to 20 % positive urine EtG and EtS tests.

The applications mentioned above show that ethyl glucuronide tests are complementary to self-reports and questionnaires, yielding valuable information on alcohol consumption which is relevant to diagnosis and therapy.

16.2.1.1 Methodical Aspects

A DRI ethyl glucuronide enzyme immunoassay (DRI-EtG EIA) is commercially available. The first study showed satisfying but not convincing results (Böttcher et al. 2008). Therefore, enquiries with medicolegal relevance need further confirmation with forensic-toxicologically acceptable methods like LC/MS-MS (Weinmann et al. 2004). The use of penta-deuterium-labeled ethyl glucuronide as internal standard and liquid chromatography-tandem mass spectrometry (LC/MS-MS) must be considered to be a gold standard. The ionic transitions observed are m/z 221 -> 75 for EtG and m/z 226 -> 75 for d5-EtG. A simple mass spectrometry would provide less reliable evidence.

In addition, EtG can also be detected in specimen of dried blood which is of relevance for forensic investigations (Kaufmann and Alt 2008; Winkler et al. 2011).

16.2.1.2 Limitations

In recent years, the potential in vitro formation and degradation of EtG and EtS have gained attention (Helander et al. 2009; Helander and Dahl 2005; Baranowski et al. 2008; Halter et al. 2009): At first, hydrolysis of EtG caused by microbes in urinary tract infections, especially *E. coli*, was reported (Helander and Dahl 2005). Complete degradation of EtG within 3–4 days by *E. coli* and C. sordellii was confirmed by Baranowski et al. (2008). In contrast, the stability of EtS for up to 11 days could be shown (Baranowski et al. 2008). Further studies with standardized test procedures for biodegradation showed that EtS in closed bottle test (OECD 301 D) remained stable for even longer periods, whereas in the context of a higher bacterial density such as in the Manometric Respiratory Test (MRT), a reduction after 6 days was detected (Halter et al. 2009). This problem could be countered by cooling and the addition of stabilizers.

Furthermore, a recent study reported that the bacterial degradation of EtG by *E. coli* can be prevented by the use of dried urine on filter paper (Redondo et al. 2012).

16.2.1.3 Possible Influences on EtG Levels

The WHO/ISBRA Study showed that EtG urine concentrations are influenced by age, gender, cannabis consumption, and renal function. In contrast, race, nicotine consumption, body mass index, liver cirrhosis, and body water content had no significant influence on EtG concentrations (Wurst et al. 2004a). The results concerning renal and liver functions have recently been confirmed:

(a) In 14 patients with reduced renal function (Høiseth et al. 2013), prolonged elimination has been reported.
(b) In a study on 120 patients with liver diseases, severity of disease had no influence on the validity of ethyl glucuronide (Stewart et al. 2013).

The positive predictive values for patients who claimed abstinence in the last 3 days for ethyl glucuronide and ethyl sulfate were 81 % and 70 %, respectively. The negative predictive values were 91 % and 93 %, respectively. Had the patients claimed abstinence in the last 7 days, the positive predictive values would be 97 % and 80 %, respectively; the negative predictive values would each be 85 % (Stewart et al. 2013).

16.2.2 Ethyl Sulfate

Ethyl sulfate (EtS) presents a secondary elimination pathway for alcohol and is usually detectable in varying interindividual concentrations. An immunochemical detection test is currently not commercially available for EtS. For combined detection of EtS and EtG, the use of rapid LC/MS-MS procedures is routinely applied.

The formation is effected by sulfonyl transferase and the breakdown by sulfatases. The molecular weight is 126 g/mol and the molecular formula $C_2H_5SO_4H$.

Ethyl sulfate formed through conjugation of activated sulfate and ethanol in rat liver was described by Boström and Vestermark in 1960 (Boström and Vestermark 1960). Its detection in rat urine was conducted after application of ^{35}S-sulfate and ethanol on rats, with thin slice chromatography and autoradiographic proof on radiographic film (Boström and Vestermark 1960).

Schneider and Glatt (2004) developed a liquid chromatography-tandem mass spectrometry method with 2-propylsulfates as internal standard. Helander and Beck (2004) used liquid chromatography-electrospray ionization-mass spectrometry (LC-ESI-MS) in a single-quadrupole modus and D_5-ethylsulfate as internal standards for the quantification of EtS in urine samples. The disadvantage of this method is a longer period of chromatographic separation. Furthermore, the exclusive monitoring of de-protonated molecules in a single MS does not meet forensic standards (Aderjan et al. 2000; Society of Forensic Toxicologists and American Academy of Forensic Sciences and SOFT/AAFS 2006). At any rate, an additional fragment ion would be required for the verification analyses according to forensic guidelines (Society of Forensic Toxicologists and American Academy of Forensic Sciences and SOFT/AAFS 2006). Even when this requirement from forensic guidelines must not be met in clinical diagnostic, it is still in demand in workplace drug testing in the USA (SAMHSA. Mandatory Guidelines for Federal Workplace Drug Testing. Federal Register 2004). In this context, an LC-tandem-MS method with penta-deuterium EtS as internal standard and two ion transitions (Dresen et al. 2004), which can be used in forensic and medicolegal cases as well as in clinical routine (Skipper et al. 2004a), raises particular interest.

In summary, a cutoff of 0.05 mg/l for repeated alcohol intake was suggested (Albermann et al. 2012b). As for ethyl glucuronide, there is evidence of prolonged elimination in reduced renal function (Høiseth et al. 2013).

16.2.3 Fatty Acid Ethyl Esters

In recent years, the existence of fatty acid ethyl esters, non-oxidative metabolic products of ethanol in blood and various organs with reduced or deficient capacity to oxidize ethanol after consumption has been proven. Since these esters were proven to cause damage to subcellular structures, they were postulated to be mediators of organ damage.

Two enzymes catalyze the formation of FAEE: acetyl-coenzyme A:ethanol o-acyltransferase (AEAT) and fatty acid ethyl ester-synthase. FAEE synthase can be isolated from rabbit myocardium, human brain, and rat fat tissue. Two of these FAEE synthases were shown to be identical to rat liver carboxyl esterase (Tsujita and Okuda 1992; Bora et al. 1996). Furthermore, pancreatic lipase, lipoprotein lipase, and glutathione transferase were shown to possess FAEE synthase activity (Tsujita and Okuda 1992; Bora et al. 1996; Bora et al. 1989).

Fatty acid ethyl esters are formed in the presence of ethanol from free fatty acids, triglycerides, lipoproteins, or phospholipids affected by specific cytosolic or microsomal FAEE synthases or through acyl-coenzyme A-ethanol o-acyltransferase.

Detectable levels are found in blood shortly after alcohol consumption and remain positive for more than 24 h (Borucki et al. 2005).

Of 15 different FAEEs in the hair, the sum of four of these (ethyl stearate, ethyl oleate, ethyl myristate, and ethyl palmitate) is shown to function as a marker in hair analysis (Pragst and Yegles 2007). With a cutoff of 0.5 ng/ml, a sensitivity and a specificity of 90 % were reported. A differentiation between abstinent, social, and excessive drinkers appears possible (Yegles et al. 2004; González-Illán et al. 2011). However, the complex GC/MS method lacks practicability for routine use.

16.2.4 Phosphatidylethanol

Phosphatidylethanol, a phospholipid, is formed in the presence of alcohol via the action of phospholipase-D. The precursor is naturally existing lipid-phosphatidylcholine. The lipid-PEth consists of glycerol which is substituted at positions sn1 and sn2 by fatty acids and is esterified at position sn3 with phosphoethanol (Gustavsson and Alling 1987). Due to the variations of the fatty acids, various homologues of PEth can be detected. In 2010, 48 PEth homologues were described in the blood of a deceased alcohol-dependent individual for the first time (Gnann et al. 2010). The PEth homologues 16:0/18:1 and 16:0/18:2 are most prevalent, and their combined sum correlates better with PEth than PEth 16:0/18:1 or PEth 16:0/18:2 alone (Zheng et al. 2011).

Using the original HPLC methods, repeated consumption of more than 50 g alcohol over 2–3 weeks yielded positive results (Varga et al. 1998), lately even with daily consumption over 40 g (Aradóttir et al. 2004).

A recent drinking experiment with healthy persons with an alcohol consumption of 1 g/kg body weight on 5 consecutive days yielded PEth values up to 237 ng/ml (Gnann et al. 2012). Measurements were made with LC-MS/MS. In contrast in alcohol-dependent patients, the values were reported to be up to 4200 ng/ml (Helander and Zheng 2009).

Various studies found no false-positive results (Wurst et al. 2003a; Hartmann et al. 2007; Wurst et al. 2004b). A linear relationship between consumed amounts of alcohol with phosphatidylethanol values has been described (Aradottir et al. 2006; Stewart et al. 2009, 2010).

In 144 patients, Aradottir et al. (2004) reported sensitivity of PEth to be 99 %, of CDT, MCV, and GGT to be between 40 % and 77 %, as well as a correlation between the amount consumed and the PEth value. In a receiver operating characteristics (ROC) curve analysis with consumption status (active drinkers vs. abstinent drinkers) as a state variable and with phosphatidylethanol, MCV, and gamma-GT as test variables, an area under the curve (AUC) of 0.973 for phosphatidylethanol could be found; the sensitivity was 94.5 % and the specificity 100 % (Hartmann et al. 2007). The findings were confirmed in further publications (Wurst et al. 2010; Wurst and Thon 2012; Stewart et al. 2010; Hahn et al. 2012). PEth values were not influenced by liver diseases and hypertension (Stewart et al. 2009).

16.2.4.1 Methodical Aspects

Concerning the interpretation of results, it is important to acknowledge that publications before 2009 used the HPLC method in combination with evaporative light scattering detection. This method detects a sum of all PEth homologues. In contrast, the new approach is the use of LC-MS- and LC-MS/MS methods (Gnann et al. 2009). These methods facilitate detection and quantification of single homologues, if a reference is available. Furthermore, recent publications suggested LC-HRMS (liquid chromatography high-resolution mass spectrometry) method (Nalesso et al. 2011) and a metabolic approach using LC-MS-IT-TOF (liquid chromatography with quadrupole ion trap-time-of-flight-mass spectrometry) (Loftus et al. 2011). Another publication presented specific PEth antibodies which were decreased in alcohol-dependent subjects or subjects with alcohol-induced pancreatitis (Nissinen et al. 2012).

For everyday practical use, the use of dried blood spots may be of significant relevance (Faller et al. 2011). This method is suggested to have results similar to whole blood measures. Furthermore, obtaining specimen is simplified since nonmedical staff can obtain capillary blood, the risks for HIV and hepatitis C infections are decreased, and storage and transport are simplified.

16.2.4.2 Limitations

In blood and tissues containing ethanol, the formation of PEth under certain conditions may be feasible. Without influencing the PEth levels, blood samples can be stored in refrigerators for up to 72 h or frozen at −80 °C.

In vitro formation of PEth in erythrocytes has been reported after addition of ethanol (Varga and Alling 2002). Further experimental studies in rats showed that ceramide is able to block the activity of phospholipase- D and inhibits the synthesis of PEth (Pragst and Yegles 2008).

16.2.5 Hair Analyses

Hair analysis has been established to assess ethanol intake. FAEE and ethyl glucuronide (EtG), two metabolic by-products of ethanol, are gaining attention as alcohol markers in hair (Auwärter et al. 2001; Pragst et al. 2001; Appenzeller et al. 2007a; Pragst and Yegles 2007; Yegles et al. 2004; Wurst et al. 2004b; Pragst and Yegles 2008; Pragst 2006).

The time frame for the detection of alcohol consumption is longer in hair compared to blood or urine. Due to head hair growth of 1 cm per month, depending on the hair length, evidence of alcohol consumption can be found for the respective time period. The deposit of lipophilic FAEE in hair occurs in sebum (Auwärter et al. 2004), whereas hydrophilic EtG is incorporated through perspiration and/or from blood (Pragst and Yegles 2007).

Measurement of FAEE and EtG allows differentiation between chronic excessive and moderate alcohol consumption as well as abstinence or very low levels of alcohol consumption.

In a consensus from the Society of Hair Testing, an FAEE concentration of over 0.5 ng/ml hair and/or an EtG concentration of over 30 pg/ml hair is interpreted as definite evidence for excessive and regular alcohol consumption (>60 g EtOH per day) (Society of Forensic Toxicologists and American Academy of Forensic Sciences (SOFT/AAFS). Forensic Toxicology Laboratory Guidelines 2006). EtG concentration of more than 7 pg/mg is a marker for frequent alcohol use (Society of Forensic Toxicologists and American Academy of Forensic Sciences (SOFT/AAFS). Forensic Toxicology Laboratory Guidelines 2006).

The combined use of FAEE and EtG can be recommended to increase the validity of hair analysis (Pragst and Yegles 2008).

In an alcohol drinking experiment, 32 women who consumed 16 g alcohol per day had EtG values of less than 7 pg in their scalp hair (Kronstrand et al. 2012). These divergent results may be explained by the fact that EtG values lower than 7 pg/mg do not exclude alcohol ingestion. Furthermore, scalp hair was pre-analytically cut in this study, while previous studies pulverized the specimen: The preparation pre-analytically has been reported to influence the results significantly (Albermann et al. 2012a).

16.2.5.1 Other Influencing Factors

Whereas only in one case a false-positive result for EtG in hair after use of EtG containing shampoo has been reported (Sporkert et al. 2012), regular use of alcohol-containing hair tonic can lead to false-positive FAEE results (Hartwig et al. 2003). No such false-positive results are reported for EtG (Ferreira et al. 2012). Impaired kidney function may lead to higher EtG levels, as preliminary results indicate (Høiseth et al. 2013).

False-negative results for both alcohol markers can also be caused by use of hair cosmetics (Yegles et al. 2004; Hartwig et al. 2003) like alkaline hair cosmetics for FSEE or bleaching substances for EtG (Yegles et al. 2004).

The hair color and melanin content in the hair play no role, in contrast to drugs and medications (Kulaga et al. 2009; Appenzeller et al. 2007b). In segmental investigations of hair samples, a chronological correlation to drink or abstinent phase with FAEE is not possible (Auwärter et al. 2004), but for EtG, two studies have shown this to be feasible (Wurst et al. 2008d; Kulaga et al. 2009).

Altogether, hair analysis for FAEE or EtG is currently a sensible tool to clarify retrospective alcohol consumption, as shown in many studies.

16.2.5.2 Practical Use

Hair analysis for FSEE or EtG is applicable in several contexts including judging driving ability and forensic psychiatry (Wurst et al. 2008a, b; Liniger et al. 2010). Another clinical use of alcohol metabolite measures is the screening for alcohol use in medication-assisted treatment of opioid-dependent subjects (Wurst et al. 2008b, d) as mentioned above.

16.2.5.3 Alcohol Metabolites and Fetal Alcohol Syndrome (FAS)

Consumption during pregnancy can have significant consequences: the fetal alcohol syndrome (FAS) and the fetal alcohol spectrum disorder (FASD) characterized by congenital abnormalities, cognitive dysfunction, and developmental disorders. Estimations report that the prevalence of FAS and FASD is 0.2 to 1/100 live births in industrialized countries (Sampson et al. 1997; Stade et al. 2009). Direct and indirect costs add up to 24,000 Canadian dollars per affected individual as estimated by Stade et al. (2009). Total costs of FASD in Canada are estimated to amount to 5.3 billion Canadian dollars (Stade et al. 2009).

A recent study about Italian and Spanish neonatologists show the relevance: 50 % Italian and 40 % Spanish participants reported to have permitted women occasional alcohol use during pregnancy (Vagnarelli et al. 2011). Alcohol intake during pregnancy can be investigated in maternal (including hair, blood, urine) and fetal specimens (meconium) (Joya et al. 2012).

To date there is only one study from Wurst et al. (2008a) employing EtG in urine and hair in pregnant women assessing alcohol intake compared with self-reports: Women at the end of the second trimester were included. The AUDIT identified 25.2 % women consuming alcohol during the pregnancy. None of the participants scored above the gender-specific AUDIT score higher than the cutoff value of 4 points. However, according to the hair analysis, 12 women drunk more than 20–40 g alcohol per day, and four had an intake over 60 g/day (Wurst et al. 2008a).

These results support the use of direct alcohol metabolites in pregnant women since increases of % CDT (percent of carbohydrate-deficient transferrin vs. total transferrin) and its isoforms were reported for this specific population (Bianchi et al. 2011; Kenan et al. 2011). The usefulness of PEth measures during pregnancy was described in only one study so far (Stewart et al. 2010).

Studies on fetal specimen include current measures of meconium. These measures are a cumulative indicator of alcohol consumption, since it is formed between the 12th and 16th weeks of pregnancy. While the first studies investigated FAEEs concentrations, recent research focused on EtG and EtS. The largest study investigated meconium of 607 newborns. 7.9 % of specimens indicated maternal alcohol intake during pregnancy (Pichini et al. 2012). Low maternal education level and age were associated with biomarker values above the cutoff (Pichini et al. 2012). Regarding FAEEs detection, the specimen has to be investigated promptly. One study reported that negative meconium values in 19 babies turned positive within 59 h (Zelner et al. 2012). Following the authors' in vivo and in vitro studies, this change may be caused by contamination through nutritional components, postnatal feces, and ethanol-producing germs (Zelner et al. 2012). This may also be the cause for 82.8 % EtG and 22.2 % FSEE positive values in meconium, reported by another study (Morini et al. 2010a).

16.2.6 The Value of Ethanol Metabolites

In summary, specific ethanol metabolites are available which can detect the spectrum between short-term intake of small amounts and long-term use of large amounts of alcohol (Table 16.1). Cutoff values and influencing factors are summarized in Tables 16.2 and 16.3.

Appropriate methods of analysis and pre-analytics are crucial for a valid and reliable detection of markers. For ethyl glucuronide (EtG), the most frequently used marker, the best method for detection is chromatographic approach which is considered a standard method especially in forensic cases. A commercial test kit is available and contributed to wide distribution of the test. Of course, lab values always require critical reappraisal. However, EtG is detectable in urine using LC-MS/Ms even after an ingestion of low amounts of alcohol (1 g), which also occurs in some foods, drugs, and disinfectants. Individuals with the motivation to or obligation for abstinence have to be informed about these "hidden contents" to avoid involuntary intake of alcohol. For forensic purposes, the current cutoff value of 0.1 mg/L should be adapted to exclude cases of involuntary alcohol use. With respect to differences in formation and degradation, EtG and ethyl sulfate (EtS) should be analyzed together, if possible. In the absence of known influencing factors, EtG in the hair can be recommended as a marker for alcohol intake for the last 3 months. Further, guidelines for interpretations of values from international society (SOHT) are available. While positive urine values of EtG and EtS can be in accord with innocent/unintentional alcohol intake, positive values of PEth are related to previous intoxications of 0.5 % and more.

The use of dried blood spots is promising and may facilitate sample taking, storage, distribution, and decrease of infection risk.

Table 16.1 Clinically relevant options for the determination of direct biomarkers, with respect to amount and duration of alcohol intake (Modified according to Thon et al. (2013))

Duration of consumption	Amount of consumption	
	>1 g/d	>40–60 g/d
<1 day	Serum, urine: EtOH, EtG, EtS	Serum and urine: EtOH, EtG, EtS; PEth in whole blood and dried blood spots (LC-MS/MS)
>1 day	Serum, urine: EtOH, EtG, EtS	Serum and urine: EtOH, EtG, EtS; PEth in whole blood and dried blood spots (LC-MS/MS)
>14 days	Serum, urine: EtOH, EtG, EtS	Serum and urine: EtOH, EtG, EtS; PEth in whole blood and dried blood spots (HPLC LC-MS/MS)
Weeks to months	Serum, urine: EtOH, EtG, EtS	Serum and urine: EtOH, EtG, EtS; PEth in whole blood and dried blood spots (HPLC LC-MS/MS), EtG and FAEEs in hair

EtOH ethanol, EtG ethyl glucuronide, *EtS* ethyl sulfate, *PEth* phosphatidylethanol, *FAEE* fatty acid ethyl esters

Table 16.2 Clinically relevant options for the determination of direct biomarkers, with respect to amount and duration of alcohol intake (Modified according to Thon et al. (2013))

Biomarkers	Amount of consumption	Cutoff	Reference
EtG in hair	Abstinence and low intake (<10 g alc/d)	<7 pg/mg	Society of Hair Testing (2009)
	Social consumption (20–40 g/d)	7–30 pg/mg	
	Excessive drinking (>60 g/d)	>30 pg/mg	
FAEEs in hair	Repeated alcohol intake	≥200 pg/mg	Society of Hair Testing (2009)
	Excessive intake	≥500 pg/mg	
EtG in urine	Total abstinence	0.1 mg/L	Thierauf et al. (2009a, b)
	- Unintentional intake - Recent alcohol use - Longer back-dated alcohol intake in larger amounts	0.1 mg/l–0.5 mg/L	
	Unintentional intake unlikely, but possible, active alcohol intake probable	0.5–1 mg/L	
EtS in urine	Total abstinence	0.05 mg/L	Weinmann et al. (2004)
PEth	>40 g/d, more than 2 weeks of alcohol intake at least once with 1 % detectable	HPLC: 0.22 μM, LC/MS-MS: 20/30 ng/ml PEth 16:0/18:1 or 0.05 μM	Varga et al. (1998), Gnann et al. (2012), Aradóttir et al. (2004)

EtG ethyl glucuronide, *FAEEs* fatty acid ethyl esters in hair, *EtS* ethyl sulfate, *PEth* phosphatidylethanol

16.3 Traditional Biomarkers for Alcohol Consumption

Many clinical-chemical parameters show pathological changes as evidence of the biochemical burden of ethanol metabolism. None of these conventional indicators show 100 % sensitivity or specificity. Nonetheless, evidence of long-term alcohol consumption can be obtained from these state markers, especially a combination of several individual indicators.

16.3.1 Gamma-Glutamyl Transferase (γ-GT)

γ-GT is a membrane-bound glycoprotein enzyme which occurs ubiquitous in the organism, but mainly in the liver, pancreas, and renal proximal tubules. γ-GT detectable in serum arises mainly from the liver so that an increase in serum enzyme activity would be a sensitive indicator for hepatobiliary diseases. Chronic alcohol consumption induces an increase in enzyme synthesis and, through direct activation of the enzyme from membrane binding, leads to increase of γ-GT in serum. The release of enzymes through liver parenchymal damage also presents a secondary mechanism in chronic alcoholic hepatitis (Conigrave et al. 2003). To exceed the

Table 16.3 Detection of direct biomarker, with respect to amount and duration of alcohol intake (Modified according to Thon et al. (2013))

Direct biomarkers	Potential influencing factor	Influence	Reference
EtG in urine	*E. coli*, dried urine spots	No	Redondo et al. (2012)
	Grade of liver disease, smoking, BMI, body water content reduced kidney function	No	Wurst et al. (2004a), Stewart et al. (2013)
EtS in urine	*E. coli*, dried urine spots	No	Hoiseth et al. (2012)
PEth	Liver disease	No	Stewart et al. (2009)
	Hypertension	No	
	Storage of ethanol blood samples	No	Aradóttir et al. (2004)
	Refrigerator temperature, −80 °C		
EtG in hair	Hairsprays with ethanol, hair color, melanin content, age, gender, BMI	No	Ferreira et al. (2012), Kulaga et al. (2009), Appenzeller et al. (2007b), Kharbouche et al. (2010)
EtG in urine	*E. coli*, *C. sordellii*	Decrease	Helander and Dahl (2005), Baranowski et al. (2008)
	Reduced kidney function	Longer detection	Wurst et al. (2004a), Hoiseth et al. (2012)
	Chloral hydrate	False positives	Arndt et al. (2009)
EtS in urine	Reduced kidney function	Longer detection	Hoiseth et al. (2012)
	Closed bottle test (OECD 301 D)	28 days stable detection, depletion after 6 days	Halter et al. (2009)
	Manometer Respiratory Test (MRT)		
FAEEs in hair	Aggressive alkaline hairsprays	False negative	Sampson et al. (1997)
	Hairsprays with ethanol	False positives	
PEth	Ethanol-containing blood samples, storage of ethanol blood samples at RT and −20 °C	Increase	Aradóttir et al. (2004)
EtG in hair	Hairspray with EtG	Increase	Sporkert et al. (2012)
	Reduced kidney function	Increase	Høiseth et al. (2013)
	Bleaching, hair styling products	False negative	Yegles et al. (2004), Morini et al. (2010b)

EtG ethyl glucuronide, *FAEE* fatty acid ethyl esters, *EtS* ethyl sulfate, *PEth* phosphatidylethanol, *BMI* body mass index, *RT* room ambient temperature, *E. coli* Escherichia coli, *C. sordellii* Clostridium sordellii

normal values (according to Szasz, 4–18 U/l in women and, 6–28 U/l in men) requires the chronic, daily alcohol intake over at least four to six weeks. A short-term, higher alcohol burden causes no such increase (Haffner et al. 1988). Nevertheless, Anton et al. (1998) showed that the drinking intensity has more influence on γ-GT than drinking frequency. In absolute alcohol abstinence, normalization of the values occurs within three weeks to 60 days (Haffner et al. 1988).

The sensitivity of γ-GT varies, according to age, gender, and body weight, from 35 % to 85 % (von Herbay and Strohmeyer 1994). Puukka et al. (2006a) showed that γ-GT increased with age in heavy alcohol drinkers as well as moderate drinkers. In contrast, in young adults less than 30 years, even when these are alcohol dependent, the sensitivity of the markers is very low (Bisson and Milford-Ward 1994). Chan et al. (1989) traced this back to higher resistance in younger patients to damaging alcohol effects. In addition, the higher vulnerability of women to alcohol-associated liver diseases is well known (Puukka et al. 2006b). Other studies have shown a relationship between being overweight (BMI > 25) and an increase in γ-GT (Puukka et al. 2006b). γ-GT levels can also be increased by various other causes, for example, the effect of medication (such as enzyme-inducing drugs, e.g., phenytoin) and teratogens, obesity, diabetes, and cholestatic or inflammatory liver diseases. Accordingly, the specificity of 63–85 % is only relatively satisfactory, and γ-GT, in spite of its practicality as single indicator of chronic alcohol misuse and current liver diseases, is a relatively poor alcohol biomarker (Cushman et al. 1984; Neumann and Spies 2003).

16.3.2 Mean Corpuscular Erythrocyte Volume (MCV)

Measurements of MCV are common in standard investigations; an increase occurs in 4 % of the general population and in 40–60 % of patients with alcohol misuse (Wymer and Becker 1990; Morgan et al. 1981). Koivisto et al. (2006) reported definite evidence of marked dose-dependent relationship between MCV and the intensity of alcohol consumption. Increase in MCV is to be expected in long-term alcohol consumption; by contrast the values normalize slowly during abstinence over a period of 2–4 months. Compared to γ-GT, the sensitivity of MCV in screening as evidence of alcohol misuse, at least in men, is inferior. In interpreting MCV values, other causes such as vitamin B12 or folic deficiency, nonalcoholic liver diseases, reticulocytosis, and hematologic diseases should be considered.

The mechanism responsible for increasing MCV is hitherto unclear; direct hematotoxic damage or interaction of ethanol and its metabolites, especially acetaldehyde, with erythrocyte membrane has been suggested (Allen et al. 2009).

16.3.3 Carbohydrate-Deficient Transferrin (CDT)

Transferrin is the most important iron transport molecule in humans; its synthesis and glycolization occur in hepatocytes. Depending on the iron load as well as the number

and breakdown of carbohydrate chains, different isoforms can be detected. Differentiation occurs through measurements of isoelectric points (pl), whose values depend on the load of bound iron ions and number of sialin acid residuals in carbohydrate chains (Stibler 1991a; Arndt 2001). Stibler and Kjellin (1976) found abnormal isoforms with much increased pl-values over 5.65 in the liquor and serum of alcohol-dependent patients and traced this back to small levels of bound sailin acid residuals. In subsequent investigations, more precise differentiation in mono-, di-, and asialotransferrin was feasible, and all abnormal isoforms were subgrouped under CDT (Stibler et al. 1986; Helander 2003b). All abnormal transferrin molecules increase in chronic alcohol consumption (Martensson et al. 1997; Arndt 2003). Measurements with HPLC showed that, though, increased alcohol consumption lead to increased disialotransferrins, while increases in asialotransferrin occur in chronic increased alcohol consumption only (Helander et al. 2003). A variety of methods and respective reference levels for the detection of CDT is available. Hitherto, measurements of CDT using HPLC is the reference standard, with routine measurements of various enzyme immunoassays in use (Helander et al. 2003; Jeppsson et al. 1993; Helander et al. 2001). For confirmation analyses, immune electrophoresis is employed (Hackler et al. 2000), while direct CDT detection method using specific antibodies is still under development (Helander 2003b; Hackler et al. 2000).

The underlying pathomechanism for CDT development is not exactly known. Inhibition of intracellular transmission of carbohydrates to transferring by toxic effects from ethanol or acetaldehyde is presumed. Ethanol's influence on the activities of membrane-bound sialine transferases and plasma sialidases in hepatocytes has been discussed, in which an imbalance in favor of sialine acid reduction enzymes occurred (Arndt 2001, Xin et al. 1995).

There has been no agreement in previous studies concerning the correlation between CDT concentrations in serum and the absorbed alcohol amounts. Though Allen et al. (1994) showed an increase in CDT with daily consumption of 60–80 g alcohol over 7 days, other studies reported contradicting results (Lesch et al. 1996; Oslin et al. 1998; Salmela et al. 1994). Additionally, contradicting results on the effect of moderate drinking (<40 g alcohol) are found (Sillanaukee et al. 2003).

The clinical strengths of CDT as a biomarker vary depending on gender, BMI, age, nicotine abuse and anorexia (Fleming et al. 2004). Previous studies showed that CDT in men is a more sensitive indicator for alcohol-related diseases compared to women (Mundle et al. 2000; Anton et al. 2001; Huseby et al. 1997). Anton and Moak (1994) presumed that CDT values in women are increased under natural conditions but not much in increased alcohol use. Furthermore, hormonal factors appear to play a role – CDT values are definitely increased in pregnant women, but reduced in postmenopausal women (Stauber et al. 1996). Obviously in the female gender, differences in CDT serum activity depend on age as well (Whitfield et al. 1998),

Among the various conventional alcohol markers, CDT is currently considered the most useful and significant indicator (Bortolotti et al. 2006). Information on sensitivity and specificity varies, since no methodical standardization exists. Further, the heterogeneity of test populations concerning age, gender, alcohol consumption, duration of abstinence before serum extraction, as well as current

liver diseases makes the comparison with other traditional markers difficult. In selected, clinical patient groups, various test methods with specificity between 90 and 100 % with high sensitivity (50–90 %) were reported (Stibler 1991b; Kwoh-Gain et al. 1990; Stowell et al. 1997a, b).

In WHO/ISBRA Study, the sensitivity of CDT with 60 % in men was slightly less than that of γ-GT; in women the sensitivity reached only 29 % (Laposata 1999) (Conigrave et al., 2002b). False-positive increased CDT values can occur in biliary cirrhotic, autoimmune hepatitis, genetically determined transferrin variants, or the autosomal recessive inherited CDG syndrome (Stibler 1991b; Salaspuro 1999). Most patients with liver diseases have insignificantly increased CDT values so that the specificity, especially in comparison to other state markers, must be stated exceptionally high and usually reach at least 90 %. Thus, CDT could be used for detection of chronic alcohol consumption and changes in drinking patterns in these patients (Bortolotti et al. 2006; Helander and Tabakoff 1997). With a half-life of 14 days and normalization of CDT values in abstinence, evidence of drinking relapses in the post-acute phase after alcohol withdrawal treatment can be obtained (Stibler 1991b; Niemelä 2002).

16.3.4 Serum Transaminases (ASAT/ALAT)

Increases of aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT) in serum are nonspecific signs of hepatocellular damage. While ASAT is produced in the liver, skeleton, and cardiac muscle tissues, ALAT is a liver-specific enzyme. Thus, an increase in ALAT practically indicates liver diseases (fatty degeneration, tumors, metastases, cirrhosis, cholangitis). Regarding measurements of ASAT, it must be differentiated between alcohol sensitive, mitochondrial (m-ASAT), and cytoplasmic isoform (c-ASAT). Conclusions on an alcohol-induced liver damage can only be drawn from increased m-ASAT/c-ASAT quotients. Increased ASAT values would be found in alcohol-dependent patients from 39 % to 47 % (Rosman and Lieber 1994). In the WHO/ISBRA Study, sensitivity of ASAT between 23 % and 45 % (women vs. men) could be found (Savolainen et al. 1990). The toxic effects of ethanol on mitochondria lead to increased release of ASAT compared to ALAT. A ratio of ASAT/ALAT exceeding 1 (and even more so when it approaches 2) indicates a strong likelihood of an alcoholic etiology (Hannuksela et al. 2002; Savolainen et al. 1990).

In summary, the sensitivity and specificity of both enzymes as indicators for alcohol misuse are considered variable so that an interpretation of an increased serum activity is mainly meaningful in the context of other liver values (bilirubin, alkaline phosphatase, γ-GT).

16.3.5 HDL Cholesterol and Apolipoprotein

Increases in HDL cholesterol and apoprotein I/II are described in many studies as specific and sensitive indicators of chronic alcohol strain; by contrast triglycerides

and total cholesterol are nutritionally influenced. Alcohol leads to an increase in the concentrations of cholesterol and phospholipids within the HDL particles and causes a shift to bigger portions of phospholipids in richer and larger HDL_2 particles (Goldberg et al. 1995; Lucas et al. 2005).

Studies showed this phenomenon to be the basic principle for the observed cardioprotective character of moderate alcohol consumption (Clemens et al. 1986; Moore and Pearson 1986). Chronic alcohol load causes an increase in HDL over 50 mg/dl; after withdrawal and with continuing abstinence, the values normalize within 1–4 weeks (Goldberg et al. 1995; Gilg et al. 1995). The pathogenic cause for alcohol-related HDL and apoprotein increases is postulated to be an enzyme induction as well as increased lipoprotein lipase activity (Gilg et al. 1995; Hannuksela et al. 2004).

Increased HDL levels without alcohol can occur under the influence of medication (sedatives, lovastatin), pronounced underweight, and physical strain. Still, the specificity of this marker is highly esteemed; moreover, it proved itself to be practicable (Hannuksela et al. 1992a). Particularly in patients without liver damage, HDL and apoprotein I/II can be used for monitoring abstinence since changes in alcohol consumption would be accurately reflected.

16.3.6 Cholesteryl Ester Transfer Protein (CETP)

Cholesteryl ester transfer protein is a glycoprotein synthesized in the liver and catalyzed out of HDL particles through lipid diffusion into LDL particles (Hannuksela et al. 1992b). Through alcohol consumption, the plasma concentration and activity of CETP are reduced, thereby increasing HDL concentration. Moderate drinking, by contrast, hardly influence CETP activity (Lucas et al. 2005; Hultberg et al. 1991; Kärkkainen et al. 1990). According to the study from Hannuksela et al. (1992b), the sensitivity and specificity of CETP as an alcohol marker can be compared to those of MCV, γ-GT, ASAT, and ALAT. Nonetheless, the use of CETP as an indicator for alcohol misuse is limited by the complex measurement method and by the influence of drugs and various diseases.

16.3.7 β-Hexosaminidase

β-Hexosaminidase is a lysosomal liver enzyme detected in serum or urine using spectrometric methods. Stowell et al. (Stowell et al. 1997b) reported higher serum activity of this glycoprotein in alcohol-dependent patients compared to healthy controls. A daily consumption of 60 g alcohol leads to significant serum increases; even short-term alcohol load is reflected in alcohol patients by its low half-life and resulting limited normalization in values (<6.2 U/l) 2–4 days later (Hultberg et al. 1991; Kärkkainen et al. 1990). As described by Humaloja et al. (1997), the pathological mechanism in rats is the reduction in biliary elimination of the enzyme in chronic ethanol intake. The specificity of β-hexosaminidase in serum is stated to

be 91–98 %; the sensitivity is 69–94 % (Stowell et al. 1997b; Taracha et al. 2001). According to studies by Kärkkäinen and Salaspero (1991), β-hexosaminidase activity reflects recent alcohol consumption, while β-hexosaminidase in urine remains increased for longer periods after alcohol consumption.

16.3.8 Methanol (MeOH)

Methanol is a monovalent alcohol produced endogenously; under physiological conditions, the concentration in serum is between 0.5 and 1.0 mg/l. Methanol can be ingested exogenously through alcoholic drinks, fruit juice, and pectin-containing fruits (e.g., bananas or apples). The metabolism of methanol occurs in the liver through alcohol dehydrogenase (ADH), which shows a manifold increased affinity to ethanol compared to methanol even without alcohol ingestion (Rietbrock 1969). That being so, in the presence of ethanol in concentrations over 0.2–0.5 %, a competitive inhibition of methanol breakdown occurs which, in continuing ethanol availability, leads to the accumulation of endogenous methanol (Mani et al. 1970). Should the ingested alcohol also contains methanol (e.g., fruit-flavored gin, whisky), the blood levels would be potentiated even more by endogenous accumulation. The methanol levels normalize itself in alcohol abstinence within several hours to several days (Haffner et al. 1997). Early evidence of increased blood methanol levels after longer drinking periods was reported in the 1970s (Magrinat 1973), among others. In numerous studies, a coincidence between increased methanol levels and blood alcohol levels has been found. Consequently, methanol values >10 mg/l, which were not caused by normal and short term, even high alcohol load over 1.5–2.0 %, were estimated and considered as an indicator for recent alcohol misuse or longer-term alcohol consumption phase (Iffland 1993; Iffland et al. 1984). Despite its high specificity, methanol is only suitable as a short-term state marker because it is rapidly normalized. Its significance lies primarily in screening alcohol misuse in clinical as well as forensic cases.

16.3.9 Acetone and Isopropanol

Physiologic levels of isopropanol in blood are up to 0.1 mg/l acetone up to 7 mg/l (Gilg et al. 1989; Iffland and Staak 1990). Both substances are not found in alcoholic drinks. Isopropanol and acetone are in reciprocal biotransformation process, meaning isopropanol is reduced to acetone and formed, through oxidehydration, from acetone. Both processes occur via alcohol dehydrogenase. Alcohol load causes an increase in isopropanol in the blood; conversely in withdrawal acetone is increased (Gilg et al. 1995; Lewis et al. 1984). Fulop et al. (1986) found increased isopropanol and acetone levels mainly in alcohol-dependent patients with concurrent eating disorders or reduced nutritional intake. It is an established practice to pool both substances in serum concentration, and a level of 9 mg/l has been recommended (Iffland et al. 1994). Still, isopropanol and acetone

appear less convincing than methanol as alcohol markers because increased acetone levels also result from metabolic disorders like ketosis in hunger, diabetes, cooling, and heavy physical strain.

16.3.10 Combination of Individual State Markers

Since individual conventional alcohol markers were found to be insufficiently sensitive and/or specific for the recognition of alcohol misuse, several important parameters in varying combinations were investigated. The better known combinations comprised of CDT, γ-GT, MCV, and ASAT.

16.3.10.1 Gamma-Glutamyl Transferase and Carbohydrate-Deficient Transferrin

Some studies showed that the combined use of γ-GT and CDT resulted in higher sensitivity and specificity compared to the use of either one alone (Hietala et al. 2006; Chen et al. 2003). Sillanaukee et al. (2001) and Sillanaukee and Olsson (2001) reported a sensitivity of 75 % and specificity of 93 % for γ-CDT from 257 alcohol-dependent patients and 362 occasional drinkers. γ-CDT is estimated using the formula [γ-CDT = 0.8 ln(γ-GT) + 1.3 ln (CDT)]. Compared to CDT and γ-GT alone, ASAT, ALAT, or MCV showed the logarithmic transformation from γ-GT and CDT to have the best predictive value to differentiate between alcohol-dependent patients and occasional drinkers (Niemelä 2007). Values for γ-CDT correlate to current amounts of consumption, regardless of whether a heavy alcohol-dependent individual or an occasional drinker was tested (Brinkmann et al. 2000). γ-CDT can thus be used to monitor abstinence, though in continuing abstinence, the values normalize within 2–3 weeks. Considering the cost efficiency and simple application, γ-CDT appears to be a suitable indicator in clinical routine work (Figs. 16.1 and 16.2).

16.3.10.2 Alc-Index

By combining methanol, acetone/isopropanol, γ-GT, and CDT in a logistic regression formula, Brinkmann et al. (2000) developed the so-called Alc-index to differentiate between alcohol-dependent patients and nondrinkers. The basic principle for the investigations was the hypothesis that each of these alcohol markers shows overlap in values in the collective with none or low alcohol consumption and alcoholics. From the results, an Alc-index of 1.7 as cutoff was defined with a specificity of 100 % and a sensitivity of 90 % to differentiate between alcohol-dependent and non-alcohol-dependent individuals. The advantage of this index is the single cutoff point instead of four different cutoff points for individual markers.

16.3.10.3 Early Detection of Alcohol Consumption Test (EDAC)

EDAC uses results from a series of routine lab parameters to identify heavy drinkers and light drinkers in study groups. In the 1980s attempts were made using

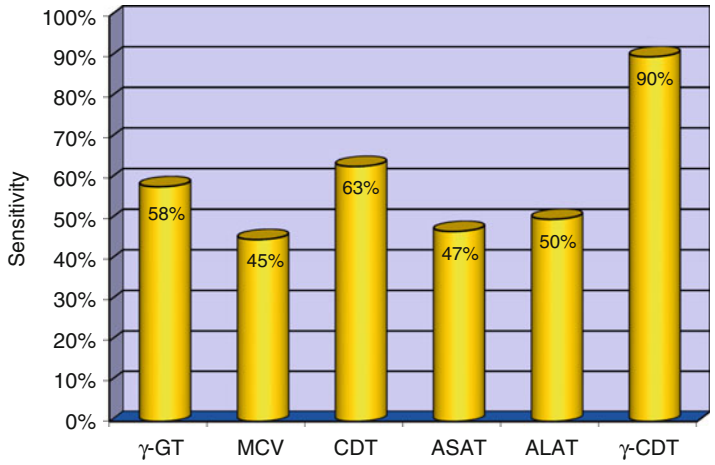

Fig. 16.1 Comparison of sensitivities of conventional markers with γ-CDT (Modified from Niemelä 2007)

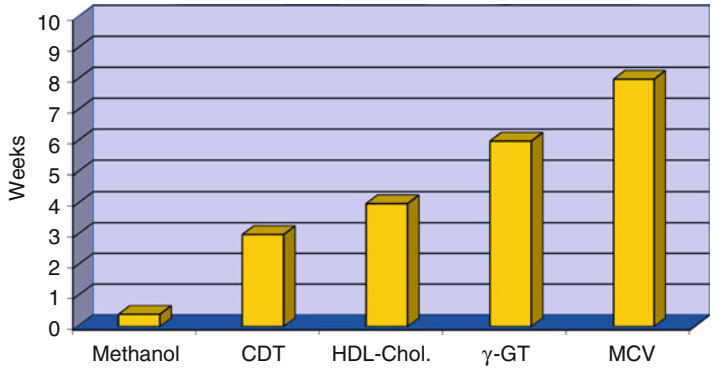

Fig. 16.2 Depiction of alcohol markers in appropriate timelines (Modified from Gilg et al. 1995)

multivariate statistical analysis to differentiate between hazardous alcohol misuse and alcohol dependence (Harasymiw et al. 2000, 2004). The use of multiple chemical and clinical parameters should reflect the physiological effects of alcohol on various organs and organ systems (Harasymiw and Bean 2007). These studies were subsequently abandoned because of the impracticability of undertaking the statistical analyses. Later, Harasymiw et al. (2000) developed the EDAC test to be an established procedure, in which a form of "mathematical fingerprint" for each tested patient could be created from 10 out of 30 routine lab values through a linear discrimination analysis. The fingerprint of an individual could possibly be that from a heavy alcoholic and presented as P-positive, representing the degree of concordance to the stereotyped alcoholic lab profile. In general, a P-positive value over

50 % showed current heavy alcohol consumption, whereas values below or equal to 50 % showed evidence of light alcohol misuse (Harasymiw and Bean 2007). The EDAC test was successfully used as screening for alcohol misuse and to identify heavy or risky alcohol consumption in various studies on different study populations (Harasymiw et al. 2000; Bean et al. 2001). Harasymiw und Bean (2007) reported higher sensitivity of 34–65 % (women/men) for EDAC test compared to 23–30 % for γ-GT in a population of 1605 heavy drinkers or probands with risky alcohol consumption. The specificity is 89 % (men) and 98 % (women). In a review from Montalto and Bean (2003), sensitivity and specificity over 80 % each was reported in the identification of alcohol misuse in heavy male and female drinkers. Given these results, the EDAC test may be a suitable way of combining routine laboratory tests for use in primary care settings. Its cost-effectiveness depends on the availability of multiple laboratory analyses, particularly using automated statistical analyses which are now available through certain providers.

16.4 Conclusion

Biomarkers are an important compliment to self-reported alcohol consumption in the diagnosis and management of alcohol use disorders. Traditional biomarkers have several limitations imposed by their sensitivity and specificity and practicability and cost-effectiveness. Combinations of these markers allow some insight into the individual's alcohol consumption over recent days and weeks. The diagnostic sensitivity of individual parameters, like ASAT or ALAT, is low; the specificity is moderately high, with the exception of CDT which shows moderate sensitivity and high specificity to differentiate between alcohol-dependent individuals and control persons. The strengths of these traditional markers lie in their practicability and, except for CDT, cost efficiency in clinical routine. Normalization of this marker occurs only after weeks or months of abstinence so that inference of current or short-term recent alcohol consumption can be made.

In contrast, direct ethanol metabolites are highly sensitive and specific, and they cover the recent time period between consumption and detection. They open new perspectives for the prevention, interdisciplinary cooperation, diagnosis, and therapy of alcohol-related disorders.

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Brief Intervention for Illicit Drug Users

17

Jennifer Harland, Linda Gowing, and Robert Ali

Contents

Abstract

Screening and brief intervention is an effective public health measure for the early detection and management of substance use disorders. There is a range of validated screening tools designed for use in various settings and contexts. This chapter provides an overview of the process that is a fundamental next step following screening, namely, the provision of an effective and targeted brief intervention for illicit drug users.

It includes an overview of the evidence related to brief interventions for people using cannabis, amphetamines, cocaine, or opiates. Although research in this area is somewhat limited, the chapter will draw on the empirical evidence for effective brief intervention in a range of areas and suggest practical approaches to engage illicit drug users. There are many possible settings (primary care, emergency department, and mental health) and various ways of presenting brief interventions,

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such as via a computer. As illicit drug use is rarely limited to one substance, implications for polydrug users are addressed. Practical steps and examples are provided, based on the principles of motivational interviewing, to demonstrate how effective brief interventions can be implemented.

Some of the common barriers to implementing brief interventions in practice will be explored. Practical solutions will be offered as a guide to overcoming both real and perceived barriers to conducting targeted and effective brief interventions in practice.

17.1 Introduction

The combination of physical, psychological, and social dimensions makes drug dependence a complex condition (Gowing et al. 2001). Addressing substance misuse is a high priority for health policy, and there are clear public health and economic benefits from the early detection of an emerging problem to prevent its escalation. Screening combined with brief intervention provides a comprehensive, integrated, public health approach across the full spectrum of substance misuse (Babor et al. 2007).

Most people with clinically significant (low-moderate severity) problems relating to their substance use will not seek help from specialist addiction treatment services (Humeniuk et al. 2012). General health-care professionals therefore play an important role in the early detection of substance misuse. Any health-care visit presents an opportunity for screening and brief intervention, and routine practice should include asking about and documenting substance use (Saitz 2010).

There is strong evidence for the effectiveness of brief interventions in primary care settings for alcohol (Kaner et al. 2008) and tobacco and growing evidence that brief interventions are effective for cannabis (Copeland et al. 2001; Copeland and Swift 2009), benzodiazepines (Bashir et al. 1994; Heather et al. 2004), amphetamines (Baker et al. 2001; 2003), opiates (Saunders et al. 1995), and cocaine use (Stotts et al. 2001). Research has shown that screening and brief intervention has led to a reduction in mortality (Cuijpers et al. 2004), health-care costs (Kaner et al. 2008), criminal justice involvement, and societal costs (Sullivan et al. 2011). The present chapter should be read in conjunction with the companion ▶ Chaps. 12, "Screening, Early Detection and Brief Intervention for Alcohol Use Disorders" and ▶ 13, "Screening for Nicotine and Drug Use Disorders."

17.2 Providing Effective Brief Interventions for Illicit Drug Users

17.2.1 Nature of Brief Interventions

The definition of brief intervention varies throughout the literature and is often used as an overarching term to include related, but slightly different, types of interventions such as brief motivation and brief motivational enhancement (Ager

et al. 2011). Overall, the goals of brief intervention are to assess and identify substance use behavior in clients, provide advice on these behaviors, facilitate behavior change with regard to substance use, and motivate the client to receive further treatment if necessary (Bien et al. 1993; Miller and Rollnick 2013). For the purpose of this chapter, brief intervention is defined as:

> A practice that aims to explore real or potential problems with substance use and help strengthen an individual's motivation to change. Brief cminterventions are generally of short duration (5–30 min) and may extend over one to four sessions (Gowing et al. 2001).

Brief intervention is time limited and structured and contains goal-oriented interventions (Babor et al. 2007). It includes clear directive advice with a focus on increasing the patient's insight and awareness regarding substance use and encouraging behavioral change through motivational interviewing and self-management approaches (Miller and Rollnick 2013). Brief interventions should be personalized and offered in a supportive, nonjudgmental manner.

The theoretical bases for brief interventions are grounded primarily in client-centered therapy, cognitive behavioral approaches, and the transtheoretical model of behavior change. As brief interventions are typically organized around a developmental theory of normative and nonnormative patterns of alcohol and other drug use, this is an appropriate theoretical framework for eliciting behavior change in brief interventions (Winters and Leitten 2007).

Generally, brief interventions are not intended to treat people with serious substance dependence; however, they are a valuable tool for intervening in problematic or risky substance use. Brief interventions can also be used to encourage those with more serious dependence to accept more intensive treatment within the primary care setting or referral to a specialized alcohol and drug treatment agency. The aim of the intervention is to help the patient understand that their substance use is putting them at risk and to encourage them to reduce or give up their substance use (Humeniuk et al. 2003).

17.2.2 Effectiveness of Brief Interventions for Alcohol and Smoking Cessation

There is a considerable range of literature on the effectiveness of screening and brief intervention. For alcohol, brief interventions shift drinking patterns in the hazardous and harmful range to a lower-risk range. A Cochrane review of screening and brief intervention for alcohol involving 29 primary care trials showed that brief interventions were associated with a significant reduction of four standard drinks per week (95 % CI 2.3–5.4) at 12-month follow-up compared with controls (Kaner et al. 2007). For smoking cessation, 17 studies of brief intervention provided by doctors found a significant increase in the odds of quitting attributable to advice (odds ratio 1.74, 95 % CI 1.48–2.05).

17.2.3 Effectiveness of Brief Interventions for Illicit Drug Users

Screening and brief intervention provided in acute care settings is associated with modest changes in self-reported recent illicit drug use (Woodruff et al. 2013). A review of randomized controlled trials of motivational interviewing among drug-abusing or drug-dependent individuals found that 14 of the 17 trials identified reported positive treatment effects (Miller et al. 2003). Among US college students, a brief intervention reduced alcohol, cannabis, and other drug use at 3 months, with greatest effects among heaviest users (McCambridge and Strang 2004); however, findings were not maintained at 12 months.

A randomized controlled trial conducted by Shetty (2011) found that a culturally competent, motivational intervention integrated into the care of vulnerable patients with facial injury reduced illicit drug use behaviors. Participants received an individualized behavioral intervention via two counseling sessions, the first shortly after their injury and the second 4–6 weeks later (Shetty 2011).

Although there is limited research on the effectiveness of brief interventions with specific illicit substances, an overview of the available evidence on cannabis, amphetamines, opiates, and prescription medications is presented below.

17.2.3.1 Cannabis

Brief interventions have shown promise among both adult and adolescent cannabis users with research to date finding brief interventions effective in reducing the quantity and frequency of use and a number of cannabis-associated problems (Carroll et al. 2006; Copeland et al. 2001; Dennis et al. 2004; Kamon et al. 2005; Stephens et al. 2000). These studies have typically compared a brief intervention (from one to six sessions) to a delayed treatment control (DTC) condition and are largely based on cognitive behavior therapy (CBT) and motivational enhancement therapy (MET).

An Australian study by Martin and Copeland (2008) found that individuals who received a single assessment session combined with a feedback session based on MET had greater reductions in cannabis use and the number of DSM-IV criteria endorsed for cannabis dependence in comparison to those in a delayed treatment control condition.

A meta-analysis of brief interventions for cannabis by the UK National Institute for Health and Clinical Excellence (NICE) found a significant increase in the likelihood of abstinence associated with brief intervention treatment (relative risk 3.33, 95 % CI 1.99–5.56) (National Collaborating Centre for Mental Health 2007). Among samples of adolescents attending emergency departments, a brief intervention with booster sessions, delivered by peers, was effective in preventing cannabis use and "days high" at 12 months (Beralnstein et al. 2009). McCambridge et al. (2008) found that there was no difference in outcome between motivational interviewing and drug information and advice at either the 3- or 6-month follow-up study interval. There was, however, substantial evidence of variability in outcomes by practitioner, regardless of the intervention being delivered, including in relation

to the primary outcome measure of reduced frequency of cannabis use at the 6-month follow-up interval (McCambridge et al. 2008).

Earlier age of initiation of cannabis use increases the severity of psychosocial and substance use problems (Walton et al. 2013). Treatment engagement among young people has been suggested to be quite low, despite reported increases in treatment uptake among adults (Copeland 2004). Time-limited brief interventions may be efficacious in engaging young people who are resistant to long-term treatment (Martin and Copeland 2008). Simply providing advice may be an effective brief intervention with young cannabis users (McCambride et al. 2008).

17.2.3.2 Amphetamines

In a randomized controlled trial of regular amphetamine users, Baker et al. (2001) reported that a brief intervention ($n = 32$) consisting of either a two-session intervention of motivational interviewing and cognitive behavioral therapy or a four-session intervention consisting of a motivational interview and skills training in avoidance of high-risk situations, coping with cravings, and relapse prevention was feasible among regular users of amphetamine when compared with the control group ($n = 32$) who received a self-help booklet. The main finding was that more people in the intervention condition abstained from amphetamines at 6-month follow-up compared to the controlled condition (Baker et al. 2001).

In a follow-up study, Baker and Dawe (2005) reported a significant increase in the likelihood of abstinence from amphetamines among those receiving two or more treatment sessions. Reduction in amphetamine use was accompanied by significant improvements in stage of change, benzodiazepine use, tobacco smoking, polydrug use, injecting risk-taking behavior, criminal activity level, and psychiatric distress and depression level.

From the findings, Baker and Dawe (2005) recommend a stepped-care approach. A basic intervention would consist of a structured assessment of amphetamine use and related problems, self-help material, and regular monitoring of amphetamine use and related harms. Baker and Dawe (2005) suggest offering two sessions of CBT at the outset for regular amphetamine users with further treatment offered depending on response.

17.2.3.3 Cocaine

Benefits have been shown after two sessions of motivational interviewing for cocaine users with low initial motivation to change (Rohsenow et al. 2004). Platt (1997), from a review of cocaine misuse, concluded that a nonconfrontational, empathic, and mutually respective therapeutic relationship is more likely to engage those more entrenched users who are unwilling to accept that they have a problem.

17.2.3.4 Heroin

Research into brief interventions with heroin users is limited; however, a study conducted by Saunders et al. (1995) concluded that brief motivational interventions were a useful adjunct to clients on methadone programs. They found that over

a 6-month period, clients receiving brief motivational interventions directed at illicit opiate use demonstrated a greater and more immediate commitment to abstinence than those who did not receive motivational interventions. Compared to the control group (who received an educational session), the intervention group also reported more positive outcomes for abstinence, had fewer opiate-related problems, were initially more contemplative of change, complied with the methadone program longer, and relapsed less quickly (Saunders et al. 1995).

17.2.3.5 Adapting Brief Interventions to the Client

It is important to recognize that illicit substances are not taken by sharply distinct population groups and two or more substances may be used concurrently or during the same use episode (Humeniuk et al. 2012). This has an impact on the focus and content of the brief intervention as the clinician works with the client to ascertain their goals and motivation to change.

Although the underlying principles of brief interventions remain the same, it is important to consider some of the characteristic traits of drug-using groups. For example, amphetamine users are generally younger than opiate users and more sexually active, and the pharmacological effects of amphetamines may result in high levels of unsafe sex behavior (Hall et al. 1993). The majority of amphetamine users are polydrug users. Benzodiazepine use is common and is often used to assist with amphetamine-related problems (Baker and Dawe 2005).

17.2.4 Settings for Brief Interventions

Most people with substance-related problems of low to moderate severity are unlikely to approach specialist addiction treatment services but do have regular contact with their general practitioner (Humeniuk et al. 2003). Primary care is the best place to screen and offer brief interventions for people with low-moderate severity problems that are nonetheless clinically significant. Any health-care visit provides an opportunity for substance use screening and brief intervention based on motivational interviewing principles (Miller and Rollnick 2013). Primary care clinicians can play a vital role in the early detection of the problem of substance use, but there is a pressing need for an empirically verified and efficient approach to screening and brief intervention.

17.2.4.1 Primary Health-Care Settings

In the developed world, 85 % of the population visit a primary health-care clinician at least once per year (Humeniuk et al. 2003). Patients whose tobacco, alcohol, and other substance use is hazardous or harmful have more frequent consultations. Many common health conditions seen in primary care may be related to substance use, and the primary care worker can use this link to introduce screening and brief interventions for substance use. The intervention then forms part of the management of the presenting complaint.

Primary care settings provide the best context and opportunity for change over time, since patients have an expectation of preventive care and often have a long-term and trusting relationship with a clinician (Saitz et al. 2010). There is research evidence supporting the effectiveness of brief interventions that target either alcohol use or smoking in primary health-care settings (Kaner et al. 2008). Brief interventions for substances other than alcohol have also been shown to be effective in primary care settings, if culturally appropriate intervention procedures are developed (Humeniuk et al. 2003).

An annual cross-sectional study of approximately 1,000 general practitioners throughout Australia has been provided since 1998 by the Bettering the Evaluation and Care of Health (BEACH) program. Frewen et al. (2008) analyzed the BEACH data between April 2000 and March 2007 and showed that general practitioners addressed illicit drug use approximately 55,000 times per year and of these, cannabis made up 3.2 % of all encounters which specified an illicit drug. The most common response was to offer counseling (approximately 52.7 % of cannabis encounters) and referral (approximately 22.5 % of cannabis encounters), while recommending a medication for a specific cannabis-related problem was less common (approximately 9.3 % of cannabis encounters) (Frewen et al. 2008).

Patients view primary care as a credible source of advice about health risks including substance use (Humeniuk et al. 2003). Nurses comprise the greatest proportion of health-care workers and serve in a variety of settings, often in roles that are focused on health promotion and patient education. This makes practice nurses ideal providers of screening and brief intervention (Puskar et al. 2013).

17.2.4.2 Emergency Departments

Emergency departments can provide brief interventions that are directly linked to harmful consequences of substance use. Combined with the "teachable moment" or post-injury period of heightened receptivity, this environment presents an opportunity to contextualize the substance misuse problem and potentially enhances the outcomes (Shetty 2011).

Currently, evidence of the benefits of brief interventions in emergency department settings in terms of reduced alcohol and other drug use and associated injuries or high-risk behaviors is inconclusive because of variability in studies in such settings (Newton 2013): however, one study of brief interventions in hospital emergency departments linked adolescents with treatment and found decreased substance-related visits to the emergency department in the following 12 months (Tait et al. 2005).

Although screening and brief intervention for hospital patients appears to be a simple, logical, and inexpensive approach, some concerns have been raised. Saitz (2010) suggests that performance measures should assess evidence-based practices, and screening and brief interventions in hospitals are not yet evidence based. Adding validated questionnaires to busy hospital routines is not simple. Hospitals need to establish procedures to address positive results and issues around confidentiality, stigma, and discrimination (Saitz 2010).

17.2.4.3 Mental Health Settings

Mental illness is estimated to co-occur in 37 % of individuals with an alcohol use disorder and in more than 50 % of individuals with a substance use disorder (Brooner et al. 1997; Degenhardt et al. 2001). Therefore, in any screening activity, it is likely that a significant subset of people receiving a brief intervention will have a mental illness. Existing literature provides an encouraging perspective regarding the benefits of brief intervention for individuals with a mental illness (Grothues et al. 2008; Baker et al. 2002; Hulse and Tait 2002). Krupski et al. (2012) found that brief intervention may not have a differing impact based on the presence of a mental illness diagnosis.

Substance misuse is common in early psychosis and impacts negatively on outcomes. Kavanagh et al. (2004) found that many people with early psychosis and substance misuse have the skills to moderate or stop consumption and may require little or no intervention to trigger an attempt to control their substance use after an early psychiatric admission. Enhancing motivation to alter drug use and refining skills may assist this process. A brief motivational approach may help to support engagement in treatment and may also be a viable first-line intervention for substance use in early psychosis. However, as commented by Kavanagh et al., further evidence is needed to support this conclusion (Kavanagh et al. 2004).

In relation to cannabis, research suggests that brief interventions may be efficacious for reducing cannabis use in those with comorbid externalizing disorders. Dennis et al. (2004) found a brief intervention to be effective in reducing frequency of cannabis use and symptoms of dependence and/or abuse in young people with self-reported psychiatric comorbidity. The majority of this comorbidity was confined to externalizing disorders, such as conduct disorder, attention-deficit/hyperactivity disorder, and alcohol use disorders.

17.2.4.4 Use in Information Technology

Advances in information technology have seen innovative approaches to providing information and support for people aiming to reduce or stop their substance use. Research has suggested that web-based brief intervention programs may be useful in reducing substance use in young adults (Bingham 2010). Web-based brief interventions have the advantage of greater reach and increased cost-effectiveness while minimizing potential barriers, such as staff time and training (Ondersma et al. 2011).

Computer-based brief intervention has been shown to decrease cannabis related problems and other drug use in adolescent cannabis users presenting to primary care (Walton et al. 2013). This approach is especially promising for financially limited primary care settings located in socioeconomically disadvantaged areas assuming such areas have access to computers and the internet (Walton et al. 2013).

Touch-screen tablet computers have been shown to be a confidential, acceptable, patient preferred, and cost-effective method of collecting health information (Hahn and Cella 2003). They have been used effectively for depression (Proudfoot et al. 2003) and smoking cessation (Free et al. 2011) interventions. Based on these

findings, opportunities and implications for screening and brief intervention for illicit substance use via computer tablets are currently being explored.

The use of a phone application or 'app' is seen to be less confrontational than face-to-face communication, particularly if the person is uncertain whether their substance use is a problem. In Australia, the 'Night Coach' phone app developed by the Australian National Council on Drugs, offers screening via the ASSIST and a brief intervention based on the persons responses and risk category. The person is able to track the amount of money they have spent on their substance use and links are provided to specialist support and treatment services.

17.2.5 Key Principles in Conducting a Brief Intervention with an Illicit Drug User

In order to deliver an effective brief intervention, it is essential to understand the underlying principles of behavior change in the context of motivational interviewing. Motivational interviewing is a collaborative conversational style for strengthening a person's own motivation and commitment to change (Miller and Rollnick 2013). The stages of change model is useful for conceptualizing a client's motivation to address their problems as the stages reflect the person's readiness to change and are important landmarks for deciding upon appropriate intervention strategies (Leamon et al. 2005). The stages of change divides the process into five distinct stages (pre-contemplation, contemplation, preparation, action, maintenance) with stage-specific goals to achieve before progression (Prochaska et al. 1992).

Brief intervention is especially useful when working with patients in the pre-contemplation and contemplation stages, but the principles and skills are important at all stages (Miller and Rollnick 2013). The brief intervention approach suggested here is based on the motivational interviewing principles developed by Miller and Rollnick (2002, 2013).

Motivational interviewing makes use of five specific skills. These skills are used together to encourage patients to talk, to explore their ambivalence about their substance use, and to clarify their reasons for reducing or stopping their substance use. The first four skills are often known by the acronym OARS – open-ended questions, affirmation, reflective listening, and summarizing. The fifth skill is "eliciting change talk" and involves using the OARS to guide the patient to present the arguments for changing their substance use behavior (Miller and Rollnick 2002, 2013).

The transtheoretical model offers an integrative framework for understanding the process of behavior change. The stages of change represent a key component of the transtheoretical model and describe a series of changes through which people pass as they change behavior (DiClemente and Velasquez 2002). The model proposes that individuals in a change process tend to negotiate a cyclical pathway that traverses a number of recognizable change stages (DiClemente and Hughes 1990).

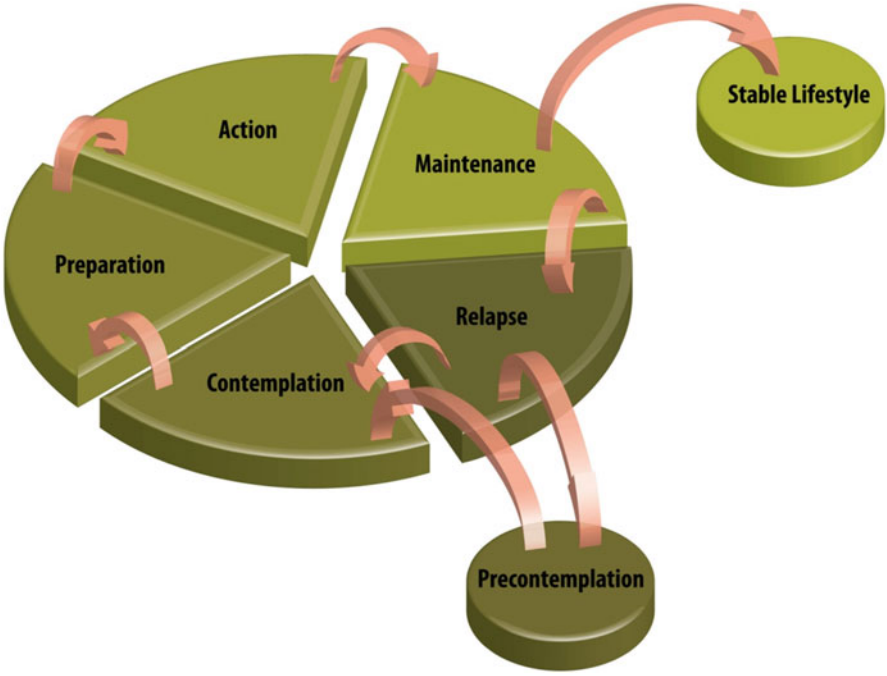

Fig. 17.1 Stages of change model (http://www.medicine.uottawa.ca/sim/data/Images/TTM_diagram.gif)

The stages of change model can be used to match interventions with a person's readiness to take in information and change their substance use (Fig. 17.1).

17.2.5.1 Linking an Appropriate Brief Intervention to the Client's Stage of Change

The multidimensional nature of drug use makes it important that drug users are assessed for motivation to change.

People in the **pre-contemplation** stage either are unaware of problem behavior or are unwilling to change. This is often expressed as "I like using" or "I do not want to stop using" (WHO 2004). People in pre-contemplation are not convinced that the negative aspects of the current behavior outweigh the positive and can be considered as "happy users" (Berridge and Robinson 2003). Individuals at this stage generally do not seek treatment unless they are coerced. They engage in little activity that could shift their view of the problem behavior and can become defensive if challenged about their behavior (Prochaska and Goldstein 1991).

The appropriate brief intervention for an illicit drug user in the pre-contemplation stage is to provide information about the effects of substance use, explore harm minimization options, and supply a list of contacts and services in case assistance is required in the future. The focus of the clinician at this stage is to

be nonjudgmental and respectful of the client's choice but at the same time raise awareness and provide relevant information (Naegle and D'Avanzo 2000). Raising doubt is an effective approach as it increases the client's perception of risks and problems with their current behavior. The overall strategy is to maintain a low intensity of interaction so the individual does not feel overwhelmed or pressured to change (Miller and Rollnick 2002).

Contemplation is a very paradoxical stage of change as, although the person is aware of a problem, they have not made a significant commitment to change (Miller and Rollnick 2002). Individuals at the contemplation stage are aware of the harms of use and the benefits of changing but are still ambivalent about changing. This can be expressed as "I don't believe how much I am spending on drugs, but I really like it" (DiClemente et al. 2004).

During a brief intervention, the clinician can be quite influential at this stage as they encourage the client to explore the risks of continued use versus the benefits of changing. The clinician can help the client "tip the balance" in favor of the most positive behavior. It is important to note that responsibility for change lies with the client and that the clinician reinforces the advantages of change and promotes self-efficacy of the client. For clinicians, it is important that they recognize ambivalence as a vital part of the contemplation stage of change. It must also be recognized that contemplation does not mean commitment (DiClemente and Velasquez 2002).

The individual has entered the **preparation stage** when they have decided to take action in the near future and are making plans and developing motivation to engage in change activities. This is often expressed as "I want to know how to give up" or "I am ready to try cutting down." The person may be confused about the best way forward and may seek advice of professional, friends, family, and people who have been through a similar experience to learn from their experience.

Individuals at the preparation stage have often sought treatment previously and may have tried and failed to change in the past. Yet, they have often learned valuable lessons from past change attempts (DiClemente and Velasquez 2002). It is important in the preparation stage to assist the client in finding the best course of action. This can be done by offering a menu of options, cocreating a plan, goal setting, demystifying the change process, and inspiring realistic hope (Prochaska et al. 1992). People at this stage may benefit from validation and reinforcement in respect to their reasons for change and assistance in planning strategies to bring about change. The overall strategy at this stage is to help the client determine the best course of action to take in seeking change.

The next stage is **action** and this is when people most overtly modify their behavior. During this stage, the person makes the move and actually implements the plan for which they have been preparing (DiClemente and Velasquez 2002). It is important that the clinician help the client to take steps toward change such as monitoring progress, reinforcing incremental success to increase self-efficacy, and helping to problem-solve as issues arise (Naegle and D'Avanzo 2000).

People at the action stage may benefit from problem-solving and goal-setting skills to assist with implementing and integrating change. They may require an introduction to the significant potential of relapse and mapping of change processes, including adjustment to the impact of change on self-identity (WHO 2004).

In the next stage, **maintenance**, the person works to consolidate the gains attained during the action stage and fights to prevent relapse. Without a strong commitment to maintenance, there will be a short lapse or relapse to the old behavior. Although traditional therapies view maintenance as a static stage, the stages of change model sees it as a critically important continuation that can last from as little as 6 months to as long as a lifetime (DiClemente and Velasquez 2002).

The maintenance stage is characterized by a substantial and sustained change of behavior and by attempts to prevent relapse or consolidate previous gains (Migneault et al. 2005). People at this stage may require assessment of the strategies that they have found useful in changing and assistance in dealing with any potential problems with sustaining the gains. They may also benefit from reinforcement of relapse prevention strategies, including returning to self-management strategies before a relapse occurs (Miller and Rollnick 2002).

The stages of change model recognizes that **relapse** is possible, and likely, when trying to change behavior. People often cycle through the stages many times before reaching their goal (Migneault et al. 2005). Therefore, a lapse should not be considered a failure but rather a minor setback. After a relapse, individuals often regress to an earlier stage and then begin progressing through the stages again. Often, people who relapse have a better chance of success the next time as they have learnt new ways to deal with old behaviors and they have history of partial success to build on (DiClemente and Velasquez 2002).

Therefore, a relapse should not be wasted as it is an opportunity for the client to refine self-management skills (DiClemente and Velasquez 2002). People who relapse need to analyze events leading up to the lapse and post-relapse impacts. Relapse is often typified by self-blame which only intensifies the impact and possible duration of the setback.

Brief Intervention in Action

Ben is a 22-year-old university student attending a large Australian university. Originally from the country, Ben has found assimilation into city living challenging. Ben lives in a share house with three older males who work as tradesmen and smoke cannabis daily. Although Ben was an occasional cannabis user in the past, his use has escalated over the past 2 years and he is now smoking daily. Ben failed two subjects in his final year and is finding it hard to stay motivated to complete his degree. Ben has not visited his family and friends “back home” for over 6 months; previously, he would make the effort and travel home fortnightly.

Ben visited the university medical center for a persistent cough. While waiting to see the doctor, Ben completed an Alcohol, Smoking and Substance

Involvement Screening Test (ASSIST) as standard procedure of the practice. Ben scored in the moderate-risk range for his cannabis use. The practice nurse engaged Ben in a brief intervention highlighting the associated risks of his current pattern of use. Although reluctant to discuss his cannabis use at first, the practice nurse was able to evoke Ben's ambivalence with his current pattern of use and offer a menu of options for him to consider. Ben's goal to complete his degree and return to his home town was the greatest motivator for change. Ben opted for online assistance and reduced his cannabis use during the following 3 months. Ben is making some positive changes by re-engaging with his family and attending lectures at university.

17.2.5.2 Conducting a Brief Intervention

As outlined in Fig. 17.2, the brief intervention is guided by the level of risk identified in the screen. Using the example of the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST), individuals who are identified in the low-risk range are encouraged to remain at this level, may benefit from general health information, and are advised of the risks of increasing their use. For people in the moderate-risk range, advice is given on the possible adverse effects of continued use, and the client's current level of concern and motivation for change is explored. The focus of a brief intervention in the high-risk range is for the client to recognize and understand the risks associated with their current pattern of use and encourage them to engage in structured treatment for their substance use.

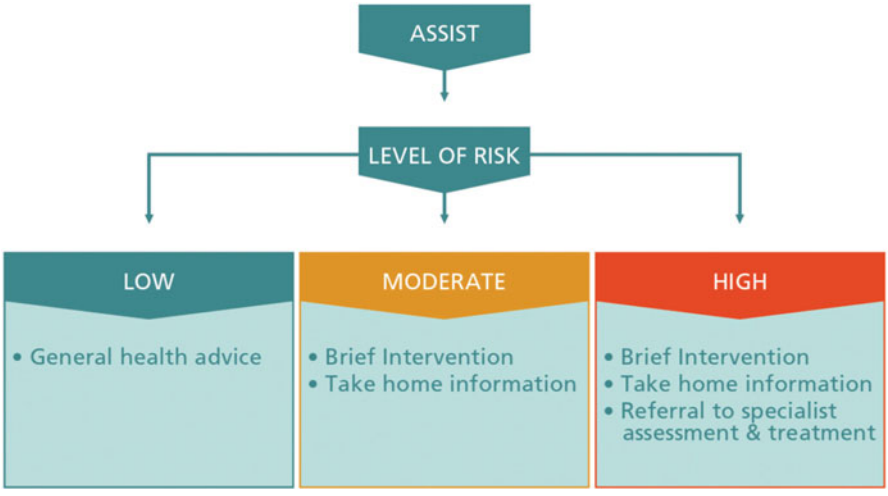

Fig. 17.2 ASSIST linked brief intervention

A useful framework to structure a brief intervention is provided by the FRAMES model. This highlights the six key components of a brief intervention: Feedback, Responsibility, Advice, Menu of options, Empathy, and Self-efficacy.

FRAMES

Feedback The provision of personally relevant feedback is a key component of brief intervention and generally follows a thorough assessment of drug use and related problems. Feedback can include information about the individual's drug use and problems from a screening instrument such as the ASSIST, information about personal risks associated with current drug use patterns, and general information about substance-related risks and harms. If the person's presenting complaint could be related to substance use, it is important to inform then about the link as part of the feedback. Feedback may also include a comparison between the person's substance use patterns and problems and the average patterns and problems experienced by other similar people in the population.

Responsibility A key principle of intervention with substance users is to acknowledge that they are responsible for their own behavior and that they can make choices about their substance use. The message that "ultimately the choice is yours" enables the person to retain personal control over their behavior and its consequences. This sense of control has been found to be an important element in motivation for change and to decrease resistance.

Advice The central component of effective brief interventions is the provision of clear advice regarding the harms associated with continued use. People are often unaware that their current pattern of substance use could lead to health or other problems or make existing problems worse. Providing clear advice that cutting down or stopping substance use will reduce their risk of future problems will increase their awareness of their personal risk and provide reasons to consider changing their behavior.

Menu of options Effective brief interventions provide the person with a range of alternative strategies to cut down or stop their substance use. This allows the person to choose the strategies which are most suitable for their situation and which they feel will be most helpful. Providing choices reinforces the sense of personal control and responsibility for making change and can help to strengthen the patient's motivation for change. Giving information or guides to cutting down or stopping is a good first start and can be used alone or in conjunction with several options.

Empathy A consistent component of effective brief interventions is a warm, reflective, empathic, and understanding approach by the person delivering the intervention. Use of a warm, empathic style is a significant factor in the person's response to the intervention.

Self-Efficacy The final component of effective brief interventions is to encourage the person to have confidence in their ability to make changes in

their substance use behavior. People who believe that they are likely to make changes are much more likely to do so than those who feel powerless or helpless to change their behavior. It is particularly helpful to elicit self-efficacy statements from patients as they are likely to believe what they hear themselves say.

17.2.6 International Perspectives and Concluding Remarks

Brief intervention following screening can make a difference by raising awareness of an individuals substance use issues and decrease risky behaviors. However, having a conversation with a person about substance use can be challenging, particularly in countries with heavy penalties for illicit drug use. This places the clinician in a perplexing situation. The clinician may be aware of the benefits of screening and brief intervention and may be keen to implement the process, but asking the screening questions may result in the mandatory reporting of the illicit drug use. How does a clinician operate within the non-maleficence principle of "*above all*, *do no harm*" when, in some countries, heavy fines, incarceration, and capital punishment are consequences of illicit drug use?

Rather than try and provide a solution to this complex dilemma, a couple of guiding principles are suggested. Above all, the clinician needs to be honest with the client about the potential consequences of their responses. Gaining trust is paramount in establishing any therapeutic relationship. Providing the client with all the necessary information related to their responses within their country's legal context is essential. Although the harmful effects of substance misuse are well known, information may not be readily available in some countries. Providing general information on the consequences of drug use may be a helpful start.

For clients who require a more complex intervention or referral into treatment, the focus of the brief intervention may be on what options are available. This may be very limited and will vary significantly between countries. When faced with mandatory reporting, the clinician may suggest reporting together and include the client in the process. This approach adheres to the client-centered principle of brief intervention and is within the legal framework of most countries. Including a treatment plan and highlighting the client's motivation to change in this process may also be helpful in the reporting process.

Barriers to effective brief interventions are not limited to countries with heavy penalties for illicit drug use. Research has found that many health-care professionals have negative or stigmatizing attitudes toward people who use substances. Some studies found that nurses had more negative attitudes than other health professionals (Howard and Chung 2000). Research has shown that nurses generally thought they had a role in screening for substance use, but not in intervention (Puskar et al. 2013).

17.2.6.1 Addressing the Barriers and Where to Go From Here

For brief interventions to become part of routine practice for health professionals, an approach at the health system level, based on the evidence, accompanied by training and promotion is needed. Continuing medical education is one way of addressing this. It is suggested that screening, brief intervention, and referral for treatment should be taught in medical school and residency (Brown et al. 2012). Similarly for nurses, the inclusion of screening and brief intervention training in undergraduate or graduate nursing curricula has been called a "next step" to improve uptake and implementation (Broyles and Gordon 2010). Attention should be paid to providing education and training about the fundamentals of brief intervention and to monitoring negative attitudes and practitioner's perceptions of their competence and confidence to deliver screening and brief intervention (Puskar et al. 2013).

The prospect of intervention early in drug use careers to curtail escalation in risk and divert away from harm is enduringly attractive (McCambridge et al. 2008). Further opportunities for brief intervention for illicit drug users need to be explored. There is a group of interventions that provide a first point of contact with drug users with the aim of providing information about drug use, particularly about approaches to reduce the risks to both the individual and the general community. In some countries, this includes peer education, clean needle and syringe distribution programs, immunization programs, and supervised injecting rooms. Outreach workers, police, and justice system personnel are also in regular contact with drug users. Although this contact may be unrelated to drug use, if drug use is identified or suspected, the contact can deliver a brief intervention or provide information about drug use and encourage engagement in treatment.

Although a strong theoretical base has been made for substance use screening and brief intervention, further randomized controlled trials are needed to determine its efficacy. Few randomized trials have addressed the question of whether brief intervention reduces illicit drug use and its consequences by identifying patients who need treatment before they seek it (Saitz et al. 2010).

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Section III

Drugs of Abuse and Pharmacotherapies for Substance Disorders

Ivan D. Montoya and Julio Bobes

Drugs of Abuse and Pharmacotherapies for Substance Use Disorders: An Introduction

18

Ivan D. Montoya and Julio Bobes

Abstract

Drug abuse continues being a public health problem. Old drugs such as alcohol, tobacco, opioids, and cannabis; newer drugs such as cocaine, amphetamines, hallucinogens, sedatives, and anabolic steroids; and the newest drugs such as the synthetic cannabinoids are producing devastating medical and psychosocial consequences among people of all ages and in most countries of the world. This section provides an overview of the pharmacological and psychosocial effects of the most common drugs of abuse as well as the state-of-the-art treatments of the addictive disorders that may result from their compulsive use. The section also includes chapters that highlight some specific therapeutic approaches, special issues related to the implementation of some treatments in some countries, and topics related to the research of new pharmacotherapies for drug addictions. In addition, this section offers a unique international perspective to these topics, which is consistent with the global nature of the drug abuse problem and responds to the need of going beyond country boundaries to effectively tackle this worldwide epidemic.

It is our pleasure to introduce the Section III of the textbook, which is titled Drugs of Abuse and Pharmacotherapies for Substance Disorders. The field of Addiction Medicine is rapidly transforming. For the most part of the last century, people with addictions were considered morally flawed and lacking in willpower. Recently,

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thanks to the great scientific advances in neurosciences, we have a better understanding of the neurophysiological basis of addiction. As a result, the concept of addiction has evolved. Addiction is now considered a medical condition associated with changes in the brain, manifested by compulsive drug use behaviors. This change in the concept of addiction has allowed scientists to explore new ways to prevent, diagnose, and treat this disorder.

Old drugs of abuse continue affecting large segments of the populations while at the same time new drugs with new challenges are constantly emerging. Old drugs such as alcohol, tobacco, opioids, and cannabis; newer drugs such as cocaine, amphetamines, hallucinogens, sedatives, and anabolic steroids; and the newest drugs such as the synthetic cannabinoids are producing devastating medical and psychosocial consequences among people of all ages and in most countries of the world. The use of old and new drugs rapidly crosses national boundaries and currently it is not possible to consider a drug use problem as specific or circumscribed to a country or a region. For that reason, it is imperative to ignore country boundaries and approach the drug use problems as global, clinical, and public health issue.

The main goal of this book is to provide a didactic and scientifically based overview of the different drugs of abuse and of their state-of-the-art treatment. It gives me a great pleasure to introduce this section because it is very comprehensive and multifaceted. The content of the chapters can be divided in three areas: (1) the specific drugs of abuse and their treatment, (2) highlights of some specific therapeutic approaches, and (3) an area that may be called "miscellaneous" because it includes a variety of topics related to the advancement of new treatments.

The first area covers the most relevant drugs of abuse and their current therapeutic approaches. It includes chapters with focus on alcohol, nicotine/tobacco, opioid, cocaine, amphetamine, cannabis, hallucinogen, inhalant, sedatives, anabolic steroid, xanthenes (including caffeine), and khat use. Unfortunately, there are no medications approved by regulatory agencies to treat the addiction to most of these drugs of abuse. For most of them, the only treatment provided is psychosocial support, which sometimes its efficacy has little or no scientific support.

Currently there are medications approved to treat alcohol, nicotine/tobacco, and opioid addiction; however, some of them are not approved in all countries. For alcohol addiction, the approved pharmacotherapies include disulfiram, acamprosate, naltrexone, and nalmefene. For nicotine/tobacco addiction, they include nicotine replacement therapies, bupropion, and varenicline. For opioid addiction, methadone, buprenorphine, buprenorphine/naloxone, naltrexone, and lofexidine are approved. Unfortunately, the number of patients who can benefit from the prescription of these medications is often limited due to multiple factors including national policies, economic constraints, and lack of clinician's expertise and confidence to prescribe them.

The second area of this section includes specific interventions that might be unique or offer new therapeutic opportunities for patients to assist them in their struggle against drug addiction. They include the pharmacological treatment of alcohol use disorders, addiction treatment with acupuncture, biologics (vaccines,

antibodies, enzymes) to treat drug addictions, buprenorphine implant in the treatment of opioid addiction, transcranial magnetic stimulation as drug addiction treatment, as well as nutrients, phytomedicines, and mind-body treatments for substance abuse. This area also covers some important experiences with specific treatments in different parts of the world such as the experience in France with buprenorphine in the treatment of opioid addiction, the experience in China and Iran with the implementation of methadone programs for the treatment of opioid addiction, and the experience in Russia with the use of naltrexone to treat opioid addiction.

The third area of this section covers aspects related to advancing the understanding of the mechanisms of action of drugs or abuse such as the enzymatic aspects of alcoholism and the risks of opioid agonist diversion. It also provides an overview of the recent advances in the research of medications to treat drug addictions as well as the regulatory aspects involved in the development and ultimate approval of anti-addiction medications by regulatory agencies, particularly the Food and Drug Administration (FDA) of the United States.

We envision that this section of the textbook will be useful to multiple readers. It is expected that clinicians at all levels of experience, from general counselors to addiction specialists, will find this section a reference to guide their clinical work and hopefully will result in improving the treatment of their patients. This section can also be useful to junior and senior investigators who may be interested in learning about the drugs of abuse and their treatment as well as the current research on pharmacotherapies for addiction and the research process required by the FDA to obtain approval. We think that students in the health-care disciplines that converge in the interdisciplinary treatment of drug addictions are an important group who will greatly benefit from this section because it provides the information in a didactic and comprehensive way. At the same time, the section gives them the opportunity to learn in more detail about some specific topics and gain an international perspective.

Finally, we want to thank all the authors who contributed to this section for their dedication and effort in writing their chapters and contributing to make this textbook an important contribution in the advancement and dissemination of the knowledge about drugs of abuse and their treatment throughout the world.

Pharmacological Long-Term Treatment of Alcohol Use Disorders

19

Karl Mann and Falk Kiefer

Contents

Abstract

The acute and long-term consequences of alcohol use disorders are very well known. Multiple treatments for these disorders have been investigated, and some of them have received approval by regulatory agencies. Disulfiram blocks the natural degradation of alcohol. It inhibits the acetaldehyde dehydrogenase, and the accumulation of acetaldehyde in the body results in unpleasant symptoms such as rush, nausea, headache, diarrhea, vomiting, and a drop in blood pressure. Disulfiram should only be prescribed once the patient has been detoxified and is free of alcohol and without withdrawal symptoms. Naltrexone is a competitive opiate antagonist with high affinity to the μ-receptor and lower affinity to the δ- and κ-receptors and is approved to treat alcohol dependence in individuals who are not opioid dependent. Acamprosate binds to NMDA receptors and thus dampens the glutamate-mediated excitability and is approved for the treatment of alcohol dependence in people who already established a state of alcohol

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abstinence. Nalmefene is the most recent medication approved for use in alcohol dependence. It was approved by the European Medicines Agency in 2012 for a reduction of heavy drinking days and/or total alcohol consumption. Nalmefene is a selective opioid ligand with an equally high affinity to the μ- and κ-receptors and medium affinity to the δ-receptor. It acts as an antagonist at the μ- and δ-receptor, but different from naltrexone, it is a co-agonist at the κ-receptor. The official indication for nalmefene is to reduce alcohol consumption. The chapter will discuss these and other medications that are being investigated for the treatment of alcohol use disorders.

19.1 Introduction

Ever since mankind realized that alcohol consumption can be accompanied by serious consequences and by what later was called impaired control, ways out of this dilemma were searched. Myths and magic around the world deal with remedies to solve or at least reduce this problem. Greek mythology has it that an amethyst helps to cope with alcohol intoxication. In the Middle Ages in France, draconian measures were taken to deal with public drunkenness. King Francois I ordered that "anyone who appeared in public in a state of intoxication should on the first occasion be imprisoned on bread and water, on the second chastised with birch and whip, and on the third publicly flogged. Should further relapses occur the delinquent was to have an ear cut off and suffer banishment" (Lewin 1931). Obviously this approach failed as so many following later. During the nineteenth and much of the twentieth century, alcoholism was considered a moral weakness. Cure was awaited from secluding individuals into asylums with strong elements of education and strengthening religious beliefs. First pharmacological attempts such as Dr. Shilo's "lemon cure" seem peculiar in retrospect. He recommended the use of 231 lemons over a period of precisely 29 days. "All five subjects developed a complete indifference to alcohol, with the craving stamped out" (Edwards 2000, 2005). Obviously this attempt did not make it into widespread use either.

In the last century, the development and testing of psychotherapies was put on the agenda. Likewise, more sophisticated pharmacological ways of securing abstinence or of reducing alcohol consumption to less harmful levels began to be considered. Some advances were based on serendipity and good clinical observation and judgment. The best-known example is the observation that workers in the rubber industry reported to feel sick when they drank alcohol. It was found that disulfiram as a by-product of rubber fabrication was released into the air and that this explained the reduction in alcohol consumption in those workers who were exposed.

As first claims for successful treatments were made, a need for standardized ways of assessing patients' improvements became evident. At the end of this process, randomized, controlled double blind trials seem the mandatory standard, although good clinical judgment keeps its place in finding new treatment options. In this chapter, we shall give an overview on currently available medications for the

long-term treatment of alcohol dependence. We concentrate on the compounds for which sufficient evidence base is available, which are approved for alcohol dependence and which are currently being used in many parts of the world. Wherever possible we concentrate on meta-analyses without referring to all the individual studies. Should there be Cochrane reviews on specific medications, our recommendations shall rely on those. The presentation of medications roughly follows the order of their approval by national or international authorities. There are a few other medications which are not approved for alcoholism but for other medical indications and which are currently suggested for an off-label use in alcoholism. These will be mentioned on a shorter note.

19.2 Pharmacological Treatment Options

19.2.1 Disulfiram

19.2.1.1 Pharmacology

As mentioned above, the potential of disulfiram (tetraethylthiuram disulfide) to modify alcohol consumption was found by serendipity. After disulfiram had been identified as the substance which caused the change in drinking habits, further research revealed the mechanism of action (Martensen-Larsen 1948). Disulfiram blocks the natural degradation of alcohol. Specifically it irreversibly inhibits the acetaldehyde dehydrogenase for 2–5 days, a condition which is only terminated by de novo synthesis of the enzyme. The accumulation of acetaldehyde in the body results in unpleasant symptoms such as rush, nausea, headache, diarrhea, vomiting, and a drop in blood pressure. Similar symptoms can be seen in about 50 % of the Asian population with a genetically determined lack of an ISO-enzyme of the acetaldehyde dehydrogenase which again leads to an accumulation of acetaldehyde when alcohol is consumed.

19.2.1.2 Indications and Contraindications

The indication for severe alcohol dependence is clear. Disulfiram should only be prescribed once the patient has been detoxified and is free of alcohol and without withdrawal symptoms. Several contraindications need to be taken into account: cardiomyopathy, coronary heart disease, severe heart arrhythmia, esophageal varicosis, hypothyroidism, and advanced arteriosclerosis. Disulfiram should also not be prescribed when patients suffer from asthma bronchiale, decompensated liver cirrhosis, and severe hypotonia. Accumulation of acetaldehyde in the human body as mentioned above can lead to very aversive reactions including death in a number of cases where the administration of disulfiram was not sufficiently supervised. Therefore, disulfiram should only be prescribed by doctors who are well aware of its potential but also of its risks and who have ample experience with the drug. For this caveat many colleagues consider disulfiram only as a “second choice treatment”; others prescribe it quite regularly (Brewer 1993).

19.2.1.3 Dosage and Undesired Effects

The dosage of disulfiram has to be tapered up starting with 250 mg in the first day moving to 500 mg as of the third day of treatment for maintenance dosage. Higher doses up to 1,000–1,500 mg might be appropriate when patients take the pill every second day (Mon-Wed-Fri). The drug should be taken orally; attempts with subcutaneous implants were not really convincing in the long run (Marie 1955). Originally patients were asked to drink alcohol after having taken disulfiram. Under supervision they should thus experience the aversive effects of the drug when alcohol is consumed. Later studies indicated that this test is not mandatory. Disulfiram worked as well without it (Krampe et al. 2006). If no alcohol is consumed, the most important side effect is sedation and initial sleepiness. However, this is transient in most cases and therefore no real reason for concern.

19.2.1.4 Efficacy

An early meta-analysis showed the superiority of disulfiram over placebo (Agosti 1995). However, this result was questioned by a large randomized trial in the USA where no significant benefit was found (Fuller et al. 1986). While this trial was very influential in some parts of the world, it did not convince clinicians who had long worked with this drug especially after some of the earlier safety issues had been resolved (Chick 1999). In Germany, disulfiram witnessed a renaissance after a group at Göttingen University published a long-term study with extremely ill patients who had been coming into the clinic literally every day for supervised intake for more than a year (Krampe et al. 2006). So far we have only limited evidence on disulfiram from head-to-head comparisons with other anticraving medications. Some publications point to a superiority over other approved medications such as acamprosate and naltrexone (Besson et al. 1998; De Sousa 2004; Laaksonen et al. 2008). This was reflected in several meta-analyses as well (i.e., Berglund et al. 2003).

19.2.2 Naltrexone

Naltrexone is the second drug which was approved for the long-term treatment of alcoholism. Based on observations in monkeys (Altshuler et al. 1980), two clinical trials were undertaken in the USA which showed a benefit over placebo (Volpicelli et al. 1992; O'Malley et al. 1992) and convinced the FDA to grant a rapid approval.

19.2.2.1 Pharmacology

Naltrexone is a competitive opiate antagonist with high affinity to the μ-receptor and lower affinity to the δ- and κ-receptors. The consumption of alcohol increases the release of brain endorphin (Gianoulakis et al. 1996) and subsequently of dopamine which results in the positive reinforcing effects of alcohol. A specific blockade of the μ-receptors and thus of the positive reinforcement of alcohol is the most likely explanation of naltrexone's clinical efficacy (Sinclair et al. 2002; Heilig et al. 2011). Although the plasma half-life of naltrexone and its active metabolite

ß-naltrexol is only about 10–12 h, its μ-receptor occupancy shown with PET studies lasts for about 48–72 h (Lee et al. 1988). For the specific impact of a polymorphism of the μ opiate receptor gene, see below.

19.2.2.2 Indications and Contraindications

Naltrexone has been approved for the treatment of drug and alcohol dependence. When prescribing naltrexone, it is important to assure that there was no recent opioid consumption either as pain medication or consumed illegally.

19.2.2.3 Dosage and Undesired Effects

While dosages of 100 g and more have been tested, it is a broad consensus nowadays that a daily dosage of 50 mg which means one pill a day is sufficient in the treatment of alcoholism. Nausea, dizziness, headache, and insomnia are the most prevalent side effects of naltrexone. In the USA, naltrexone carries a box warning by the FDA due to its potentially aggravating effects of alcoholic liver dysfunction.

19.2.2.4 Efficacy

The two pivotal trials (Volpicelli et al. 1992; O'Malley et al. 1992) were followed by many more studies around the world (Mann 2004). More than half of them showed significant superiority over placebo. Those which did not were often not powered well enough, were done in difficult to treat patients (Krystal et al. 2001), or had a very high placebo response (Gastpar et al. 2002; Mann et al. 2013). Recent meta-analyses and a Cochrane analysis conclude that there is a clear benefit of naltrexone in the treatment of alcoholism (Rösner et al. 2010a, b). A genetic component in treatment response was first demonstrated in a post hoc analysis of three independent trials (Oslin et al. 2003). Patients were genotyped looking for carriers of the Asp40 allele (A/G, G/G) versus individuals carrying the Asn40 allele (A/A). The positive treatment effect was confined to patients who carried at least one G allele. This finding has been replicated several times (Anton 2008) but remains somewhat controversial due to negative studies (Gelernter et al. 2007).

19.2.3 Acamprosate

Acamprosate, a calcium-bis-acetylhomotaurinat, was first discovered and tested in France (Lhuintre et al. 1985; Mann 2004). The results of several clinical studies led to an approval in most European countries in the mid-1990s. The approval in the USA followed about a decade later.

19.2.3.1 Pharmacology

Acamprosate is the calcium salt of N-acetyl homotaurine, a small, highly flexible molecule with similarities to many amino acids, most notably glutamate, gamma-aminobutyric acid, aspartate, glycine, and taurine (Spanagel and Zieglgänsberger 1997; Spanagel and Kiefer 2008). Its mechanism of action seems to be linked to

a high activity of the glutamatergic system in alcoholics. Acamprosate binds to NMDA-receptors and thus dampens the glutamate mediated excitability (Spanagel and Mann 2005). There are some reports about a binding of acamprosate to the polyamine site of the NMDA receptor as well as binding to the mGluR5 receptor (Harris et al. 2002). It could be shown that a blockade of the mGluR5-receptor reduced the self-administration of alcohol in free-choice paradigms in animal models (Spanagel and Mann 2005). Although most recent work has focused on the glutamatergic system, homotaurine is a known GABA(A) receptor agonist, and studies on neuronal networks in vivo suggest that acamprosate may have differential effects on glutamate/NMDA receptors at low concentrations, with effects on GABA(A) receptors at higher concentrations (Pierrefiche et al. 2004). Some data suggest that acamprosate dampens alcohol-induced dopamine release (Cowen et al. 2005). The same could be true in conditioned withdrawal situations. This would mean that acamprosate also acts via a blockade of the reinforcing effect of alcohol (for a more exhaustive discussion of acamprosate's potential mechanisms of action including its neuroprotective effects, see de Witte et al. (2005) and Mann et al. (2008).

19.2.3.2 Indications and Contraindications

Acamprosate is approved for the treatment of alcohol dependence. It is supposed to be prescribed for the maintenance of an already established state of abstinence. Contraindications are pregnancy and lactation as well as renal insufficiency with serum creatinine levels of more than 120 µmol/l.

19.2.3.3 Dosage and Undesired Effects

The daily dosage of acamprosate is 1996 mg (three times two tablets). Since it takes several days until clinically meaningful brain concentrations are established, the treatment should begin as soon as possible. Acamprosate does not interact with other medications and does not influence alcohol toxicity. Its main side effects are diarrhea and other gastrointestinal symptoms as well as headache and pruritus.

19.2.3.4 Efficacy

There have been a large number of randomized controlled trials worldwide testing acamprosate against placebo (Kiefer and Mann 2010). The majority showed a significant benefit of acamprosate. This is corroborated by Cochrane analyses, the latest of which was published in 2012 (Rösner et al. 2010a, b). However, there were several negative studies as well such as the large COMBINE study in the USA (Anton et al. 2006) and more recently by Mann et al. (2013). Based on its potential mechanism of action described above (dampening of a hyper-glutamatergic state) it was speculated that acamprosate could be more beneficial in severely affected patients who are more likely to suffer from an upregulated glutamate system (Spanagel and Kiefer 2008). Our own study with a head-to-head comparison of two cohorts of patients who differed in severity measures did not support this assumption (Mann et al. 2013). Another idea according to which acamprosate

would be more beneficial to individuals who relapse for the negative reinforcing effect of alcohol (Verheul et al. 1999; Mann et al. 2009; Heilig et al. 2011) still awaits empirical support. The first studies aiming to associate acamprosate's efficacy with genetic markers suggest an involvement of a single-nucleotide polymorphism located in the *GATA binding protein 4* (*GATA4*) gene (Kiefer et al. 2011). *GATA4* represents a factor regulating the transcription of ANP and showed an association with alcohol dependence in two independent genome-wide association studies on alcohol dependence (Treutlein et al. 2009; Edenberg et al. 2010).

19.2.4 Nalmefene

Nalmefene is the most recent medication approved for use in alcohol dependence. It was approved by the European Medicines Agency in 2012 for a reduction of heavy drinking days and/or total alcohol consumption.

19.2.4.1 Pharmacology

Nalmefene is a selective opioid ligand with an equally high affinity to the μ- and κ-receptors and medium affinity to the δ-receptor. It acts as an antagonist at the μ- and δ-receptors, but different from naltrexone, it is a co-agonist at the κ-receptor (Bart et al. 2005). Studies in rodents seem to show that the difference compared with naltrexone concerning the action at the κ-receptor might be of relevance lending the drug higher potency in animals with more severe dependence (Walker et al. 2011). However, this finding needs to be replicated in humans.

Nalmefene has several metabolites which have much less affinity to the μ-receptors than the parent substance. Only nalmefene 3-O-sulfate contributes to the pharmacological effect, but this metabolite is only present in low concentrations. Nalmefene has a plasma half-life of 10–12 h. Blockade of brain receptors with nalmefene lasts between 48 and 72 h.

The mechanism of action is mainly based on its antagonistic properties at the μ-receptor. This counteracts the reinforcement driven by an alcohol-triggered mesolimbic dopamine release which is facilitated by the release of ß-endorphins. In studies with animal models, an additional effect based on nalmefene's role as a partial κ-receptor agonist (Walker et al. 2011) was observed. This is currently being investigated in humans.

19.2.4.2 Indications and Contraindications

The official indication for nalmefene is to reduce alcohol consumption (number of heavy drinking days, total alcohol consumption) in alcohol-dependent patients who have a high drinking level according to the World Health Organization (WHO 2000: men >60 g/day and women >40 g/day) and continue to have this level 2 weeks after the initial assessment. It is important to ensure that patients have not recently consumed opioids either as pain medication or illegally.

19.2.4.3 Dosage and Undesired Effects

The dosage per day is 20 mg, but nalmefene can be taken as needed. Dizziness, nausea, and insomnia are the most prevalent side effects. In the recent clinical trials, these were mild to moderate and mostly transient.

19.2.4.4 Efficacy

Several earlier studies indicated its efficacy in reducing consumption in alcohol-dependent patients (Mason et al. 1999; Karhuvaara et al. 2007). One study did not show a significant effect (Anton et al. 2004). Recently three large-scale phase III studies were conducted in Europe which showed efficacy over placebo in reducing heavy drinking days and total alcohol consumption; all three studies are published (Mann et al. 2013; Gual et al. 2013; van den Brink et al. 2013).

19.2.5 Topiramate

This medication is approved for the treatment of epilepsy. Its use in alcoholism has been tested because of indications that it reduces the reinforcing effects of alcohol and inhibits glutamatergic pathways in the corticomesolimbic system (Johnson 2005; White et al. 2004). A first positive single-site trial (Johnson et al. 2003) was followed by a larger multisite trial (Johnson et al. 2007). This latter showed a significant effect over placebo in reducing alcohol consumption. Patients did not have to be abstinent to participate which was different from many other studies referred to in this chapter (with the exception of the nalmefene trials, see above). The effect size was considerable, but undesired effects were as important as expected. Therefore, the medication had to be carefully titrated from week 0 to week 5. Undesired effects were paresthesia, headache, taste perversion, fatigue, and difficulty with concentration and memory. A smaller and more recent study did not show a significant effect (Likhitsathian et al. 2013). However, as expected the first meta-analysis comes to a positive overall effect of the drug (Arbaizar et al. 2010). In conclusion, off-label use may be worth trying but only with a titration of the dose and under very careful consideration and monitoring of these side effects (Aubin and Daeppen 2013).

19.2.6 Baclofen

Baclofen acts as an agonist at the B subunit of GABA receptor (GABA-B). Since GABA neurotransmission is known to be involved in the regulation of anxiety as a common symptom in patients being treated for alcohol withdrawal and alcohol dependence, baclofen was repeatedly tested in alcohol-dependent subjects (Addolorato and Leggio 2010). Recently, Brennan et al. (2013) assessed the benefit of baclofen for alcohol dependence in a review of the literature based on randomized controlled trials and case series. Although primary outcomes

differed between trials, patients treated with baclofen (30 mg) experienced higher rates of abstinence from alcohol than those taking placebo in the majority of case series and two of the randomized controlled trials (Addolorato et al. 2002, 2007). Data suggest that baclofen was safe in patients with alcohol dependence, including those with moderate to severe liver cirrhosis and may provide beneficial anxiolytic effects. However, the largest available randomized controlled trial by Garbutt et al. (2010) failed to show a benefit for 30 mg baclofen in assessing the efficacy and safety in terms of weekly heavy drinking days and percentage of abstinent days or for the secondary outcomes of craving, for example, depression. Again, baclofen was well tolerated with no significant reported adverse events.

Taken together, positive effects from using baclofen for the treatment of alcohol dependence can be surmised; however, the small number of studies currently does not allow a final conclusion. Larger trials that include higher dosages of baclofen (up to 270 mg daily) are currently ongoing.

19.2.7 Combining Anticraving Medications

There were a number of attempts to combine anticraving medications. The most important maybe were testing acamprosate plus naltrexone versus placebo or versus each single medication. While a first combination study (Kiefer et al. 2003) showed a benefit of the combination over placebo, an Australian study (Morley et al. 2006) and the COMBINE study (Anton et al. 2006) were not able replicate this finding. However, treatment groups differed markedly, and the role of detoxification and abstinence when starting medication as well as the role of the interaction with concomitant psychotherapy remain to be determined. At least two comparisons of acamprosate and/or naltrexone with disulfiram point to a higher efficacy of disulfiram (Besson et al. 1998; Laaksonen et al. 2008), but these studies had to be done single blind with all the limitations involved here. In conclusion, to date a combination of anticraving medications in uncomplicated alcoholics (no depression, etc.) does not seem overly convincing.

19.2.8 Additional Psychosocial Treatment

Some kind of counseling to ensure motivation and compliance was mandatory in almost all of the trials referred to in this chapter. In most cases this additional psychosocial treatment was manualized, and staff had to be trained to deliver it (Starosta et al. 2006; Pettinati et al. 2004; Johnson et al. 2007; Brüeck and Mann 2006). It varied in intensity with no hint that more is better (see COMBINE study, Anton et al. 2006). For clinical practice this means that some kind of counseling including advice and maybe motivational elements is recommended when these medications are prescribed to alcohol-dependent patients.

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Enzymatic Aspects of Alcoholism-ADH and ALDH

20

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Contents

Abstract

Most ethanol taken into the body is converted to acetaldehyde by alcohol dehydrogenase (ADH), and then from acetaldehyde to acetic acid by aldehyde dehydrogenase (ALDH). However, polymorphisms exist in the genes of these enzymes. A super-active form of ADH1B and an inactive form of ALDH2 have preventive effects against alcoholism. In addition, several reports have suggested an association between polymorphisms in ADH1C, ADH4, and ALDH1A1 and alcoholism. Moderate to heavy drinkers with inactive ALDH2 and less-active ADH1B have a much higher risk of gastrointestinal tract cancer compared with those with active ALDH2 and super-active ADH1B. The ADH1B and ALDH2 polymorphisms are associated with various physical diseases such as liver disease, pancreatitis, and diabetes mellitus. Alcoholics with inactive ALDH2 have unique clinical characteristics; for example, they

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develop alcoholism more slowly. Inactive ALDH2 is thought to cause high blood acetaldehyde concentrations and a painful flushing response, which suppresses alcohol consumption. However, the mechanism by which super-active ADH1B decreases alcohol consumption and the risk of alcoholism remains unclear. Identifying ADH1B and ALDH2 genotypes might be useful in the prevention and treatment of alcoholism.

20.1 Introduction

Most alcohol taken into the body is eliminated in the liver; first, ethanol is converted to acetaldehyde by alcohol dehydrogenase (ADH), and then acetaldehyde is converted to acetic acid by aldehyde dehydrogenase (ALDH). These enzymes have genetic polymorphisms that can alter the activity of alcohol and acetaldehyde metabolism. These polymorphisms are known to have a great effect on drinking behavior in healthy people as well as on the risk of alcohol dependence. Moreover, variations in metabolic enzymes are associated with the risk of physical diseases, including gastrointestinal tract cancer and liver cirrhosis, in moderate to heavy drinkers. Several studies have suggested that the clinical characteristics and disease course of alcohol dependence differ between the ADH and ALDH genotypes. In this chapter we review variations in alcohol-metabolizing enzymes and alcoholism.

20.2 Polymorphisms of Alcohol Metabolizing Enzymes and Alcoholism

20.2.1 Alcohol Dehydrogenase (ADH) and Alcoholism

More than 90 % of alcohol taken into the body is eliminated via the liver. Three mechanisms mediate the oxidation from ethanol to acetaldehyde: ADH, the microsomal ethanol oxidizing system (MEOS), and catalase. ADH works at low to high concentrations of alcohol and plays a major role in alcohol metabolism. MEOS works only at high concentrations of alcohol. Catalase is considered to have a minor effect on alcohol metabolism.

There are five classes of ADH (class I–V), encoded by seven genes (ADH1A, ADH1B, ADH1C, and ADH4–7). Class I ADH consists of homo- or heterodimers of α-, β-, and γ-subunits encoded by ADH1A, ADH1B, and ADH1C, respectively. Class I ADH enzymes have high affinity for ethanol and contribute the most to ethanol metabolism in the liver. Class II ADH, which is a homodimer of two π subunits encoded by the ADH4 gene, has a higher K_m (the Michaelis constant) for ethanol than class I ADH, but is still believed to play some role in ethanol elimination, although the effect seems weaker than that of class I ADH enzymes. Class III (ADH5) and class IV ADH (ADH6) seem to have little involvement in ethanol oxidation. Class V ADH (ADH7) is abundant in the stomach and considered to contribute during the early stage of alcohol metabolism in the stomach

mucosa. ADH genes cluster on chromosome 4q, and some whole-genome studies suggest a link between the chromosomal region containing the ADH genes and the risk of alcoholism (Long et al. 1998; Reich et al. 1998).

There are functional polymorphic loci in the ADH1B gene: ADH1B*1, ADH1B*2, and ADH1B*3. The ADH1B*2 allele has an arginine to histidine substitution at the 48th position (rs1229984), and the ADH1B*3 allele has an arginine to cysteine substitution at the 370th position (rs2066702). The ADH1B*1 allele is common in Caucasians but occurs in only a small portion of Asians; the allele frequency of ADH1*1 is more than 90 % in Caucasians and only 30 % in Asians. In contrast, the ADH1B*2 allele is more common in the Asian population, with an allele frequency of about 70 % in Asians and about 10 % in Caucasians (Goedde et al. 1992). ADH1B*3 is comparatively common (about 15 %) in populations of African ancestry.

In vitro studies have shown that ADH homodimers that consist of beta subunits encoded by the ADH1B*2 allele are "super-active" in ethanol oxidization, much more so than those encoded by the ADH1B*1 allele (Yoshida 1994). Similarly, homodimers composed of the subunit encoded by the ADH1B*3 allele are more active in ethanol oxidization than the ADH1B*1. The impact of ADH polymorphism on alcohol metabolism in humans is not clear. A few studies that measured blood alcohol and acetaldehyde concentrations after oral administration of ethanol in Japanese subjects showed that there was little difference in the alcohol elimination rate and peak blood acetaldehyde concentrations among the three ADH genotypes, that is, ADH1B*1/1, ADH1B*1/2, and ADH1B*2/2 (Mizoi et al. 1994). In contrast, a few studies with African-American subjects reported that individuals with the ADH1B*3 allele have a higher alcohol elimination rate than those without the ADH1B*3 allele (Thomasson et al. 1995). However, the oral administration challenge has methodological limitations in that it is difficult to evaluate the diffusion of ethanol into various organs. A study using the alcohol clamping method, in which ethanol was administered to Jewish subjects by intravenous infusion, showed a higher alcohol elimination rate in individuals with the ADH1B*2 allele than in those with the homozygous ADH1B*1 allele (Neumark et al. 2004). Birley et al. studied the association between alcohol elimination rate and single nucleotide polymorphisms (SNPs) in ADH genes clustering in chromosome 4 and reported that a number of SNPs revealed allelic associations with alcohol metabolism, but the effect of Arg48His polymorphism in the ADH1B gene was minimal (Birley et al. 2009).

The super-active form of ADH1B is known to have preventive effects against alcoholism. Genetic studies have shown the allele frequencies of ADH1B*2 are lower in alcoholics than in controls (Table 20.1). The frequencies of ADH alleles differ among ethnic groups, but differences in ADH allele frequency between alcoholics and controls have been confirmed in several ethnic groups (Higuchi et al. 2004). The frequency of the ADH1B*3 allele has also been reported to be significantly lower in alcoholic subjects than in controls, as was shown with the ADH1B*2 allele (Edenberg et al. 2006).

The mechanism by which the super-active form of ADH1B decreases the risk of alcoholism is unclear. One possible explanation is that higher activity of ADH1B*2

Table 20.1 Comparison of allele frequencies of ADH1B and ALDH2 polymorphisms in alcoholics and controls

	No. of samples		Allele frequencies[a]		
Ethnicity	Alcoholics	Controls	Alcoholics	Controls	Study
*ADH1B*1 allele frequency*					
Chinese	47	49	0.52	0.27	Thomasson et al.
Japanese	655	461	0.48	0.25	Higuchi et al.
Chinese	545	340	0.54	0.27	Chen et al.
Caucasians	425	451	0.99	0.96	Borras et al.
Native Americans	203	137	0.95	0.91	Wall et al.
*ALDH2*2 allele frequency*					
Chinese	50	50	0.06	0.30	Thomasson et al.
Japanese	96	60	0.10	0.27	Maezawa et al.
Japanese	90	66	0.02	0.34	Tanaka et al.
Chinese	545	340	0.08	0.24	Chen et al.
Japanese	1,871	361	0.06	0.25	Nakamura et al.

Reprinted from Higuchi et al. (2004)
[a]Frequencies of ADH1B*1 and ALDH2*2 alleles

causes higher acetaldehyde production, which in turn leads to adverse effects that suppress drinking behavior. However, there is no evidence of an accumulation of acetaldehyde after alcohol intake in humans who have the ADH1B*2 allele.

The γ-subunit encoded by ADH1C has a polymorphisc loci at the 272 (rs1693482) and 350 (rs698) amino acid position in high linkage equilibrium: ADH1C*1 with 272Arg-350Ile and ADH1C*2 with 272Gln-350Val. The subunit encoded by ADH1C*2 allele has less activity during ethanol elimination. Several studies reported that the ADH1C*2 allele is associated with a higher risk of alcohol dependence than the ADH1C*1 allele (Zintzaras et al. 2006). It is suggested that this association might be due to the linkage equilibrium between ADH1C*1 and ADH1B*2; however, the association is detected even in a population that rarely has the ADH1B*2 variant (Montane-Jaime et al. 2006).

Some studies have also suggested that the variation of class II ADH encoded by the ADH4 gene is associated with alcohol dependence. An analysis of SNP markers at the ADH gene cluster on chromosome 4q22 found that the strongest association with alcohol dependence was detected at the ADH4 gene region (Edenberg et al. 2006), but the particular locus responsible for this association and its function are still unclear.

20.2.2 Aldehyde Dehydrogenase (ALDH) and Alcoholism

Most acetaldehyde produced from ethanol by ADH and other oxidizing enzymes is oxidized to acetic acid by ALDH in the liver. There are several ALDH family genes in humans, but ALDH1 and ALDH2 are the most important for acetaldehyde metabolism. It is considered that mitochondrial ALDH2 plays a major role in the

elimination of acetaldehyde, while cytosolic ALDH1A1 and mitochondrial ALDH1B1 are also involved in acetaldehyde metabolism. Both ALDH2 and ALDH1 are tetrameric enzymes composed by the subunits encoded by each allele.

The ALDH2 gene has polymorphic loci that alter the function of acetaldehyde metabolism. The ALDH2 gene is located at chromosome 12q24 and consists of 13 exons and 12 introns. This gene has a single-point mutation in the exon 12 coding region corresponding to a Glu to Lys amino acid substitution (rs671). This polymorphic site encodes active (Glu487, ALDH2*1) and inactive (Lys487, ALDH2*2) subunits of ALDH2. The isozyme containing the Lys487 subunit has no role in the elimination of acetaldehyde; therefore, it is supposed that the homozygote of the ALDH2*2 allele is not active in the elimination of acetaldehyde, and even the heterozygote is only minimally active. In fact, oral ethanol administration studies have shown that individuals with the ALDH2*2 allele have higher peak blood acetaldehyde concentrations after ethanol intake than those who have only the ALDH2*2 allele (Luu et al. 1995). This polymorphism is found only in East Asian populations.

Individuals whose genotype contains the ALDH2*2 allele suffer a "flushing" response upon drinking. The flushing response is an adverse effect of alcohol due to its high acetaldehyde concentration. The response includes unpleasant symptoms such as facial flushing, nausea, headache, palpitations, and rapid heartbeat. Individuals with homozygotes of the ALDH2*2 allele have a severe flushing response after a small amount of ethanol intake and even those with heterozygotes experience these symptoms when they drink large amounts of alcohol.

The ALDH2 polymorphism is associated with drinking behavior and furthers the risk of alcoholism. It is reported that the ALDH2*2 genotype has a strong influence on drinking patterns and alcohol consumption levels in healthy people (Higuchi et al. 1996). Moreover, genetic association studies have shown that the ALDH2*2 allele has a preventive effect on the risk of alcoholism (Higuchi et al. 2004). The allele frequencies in an East Asian population range from 0.24 to 0.34, whereas the allele frequencies in East Asian alcoholics range from 0.02 to 0.10 (Table 20.1). The mechanism of this effect is considered to be that the discomfort associated with the flushing response after alcohol consumption prevents individuals from drinking heavily.

Several genetic association studies between ALDH1A1 polymorphism and alcohol dependence have been conducted. The ALDH1A1 gene has two polymorphic loci in the promoter region – ALDH1A1*2, a 17-bp deletion, and ALDH1A1*3, a 3-bp insertion – and transfection assays suggest that these polymorphisms might be functional (Spence et al. 2003). Polymorphisms in the ALDH1A1 gene are reported to be associated with the risk of alcohol dependence and drinking behavior (Ehlers et al. 2004). A possible explanation for this association may be that the deficiency of ALDH1A1 activity causes flushing similar to that seen with inactive ALDH2.

20.2.3 ALDH2 and ADH1B Polymorphism and Cancer

Alcohol consumption is known to increase the risk of several types of cancer, including esophageal, pharyngeal, colorectal, and breast cancer. Many studies have

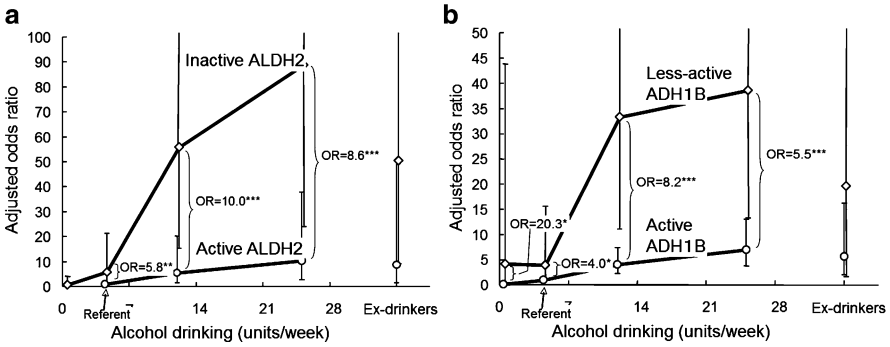

Fig. 20.1 Alcohol consumption and the risk for esophageal squamous cell carcinoma according to (**a**) ALDH2 genotype and (**b**) ADH1B genotype. The subjects were classified as never/rare drinkers; current drinkers who consumed 1–8.9 units/week (light drinkers; 1 unit = 22 g ethanol), 9–17.9 units/week (moderate drinkers), or 18+ units/week (heavy drinkers); or ex-drinkers. Odds ratios were adjusted for age, frequency of drinking strong alcoholic beverages straight, pack-years of smoking, frequency of intake of green and yellow vegetables, and frequency of fruit intake. The *vertical lines* indicate the 95% confidence interval. *$p<0.05$, **$p<0.01$, and ***$p<0.001$ (Reprinted from Yokoyama et al. 2010)

shown that ALDH2 deficiency increases the carcinogenic effect of alcohol in moderate to heavy drinkers (Yokoyama et al. 2010). Figure 20.1a shows the relation between the risk of esophageal squamous cell carcinoma and the amount of alcohol consumption in the individuals with active ALDH2 (ALDH2*1/*1) and inactive ALDH2 (ALDH2*1/*2). A case-control study of Japanese esophageal squamous cell carcinoma patients and controls demonstrated that moderate drinkers (198–365 g ethanol/week) with inactive ALDH2 had a 55.8-fold greater risk of this cancer than never/rare drinkers (<22 g ethanol/week) and that risk far exceeded the odds ratio of 10.4 of heavy drinkers (≥396 g ethanol/week) seen in the active ALDH2 group (Yokoyama et al. 2002). Similarly, a meta-analysis reported a higher risk of head and neck cancer, including oral, pharyngeal, and larynx cancer, in the inactive ALDH2 group than the active ALDH2 group among moderate (odds ratio: 1.68) and heavy drinkers (odds ratio: 3.57) (Boccia et al. 2009). The association between ALDH2 and esophageal cancer is considered to be due to the carcinogenicity of acetaldehyde. The high acetaldehyde concentration in the esophagus of individuals due to the lack of ALDH2 activity causes DNA damage and further carcinogenesis.

The ADH1B polymorphism is also associated with the risk of esophageal cancer. Individuals with the less-active form of ADH1B have a higher risk of esophageal and oropharyngeal cancer compared with those who with super-active ADH1B (Fig. 20.1b). Unlike ALDH2, the association between ADH1B and esophageal cancer seems unclear, because there is little evidence that the ADH1B polymorphism affects acetaldehyde concentration. One possible explanation might be that ethanol and acetaldehyde remain at higher levels in the blood and saliva for longer periods in individuals with less-active ADH1B than in those with super-active ADH1B.

20.2.4 ADH1B and ALDH2 Polymorphism and Physical Diseases

The ADH1B and ALDH2 polymorphism are associated with various physical diseases such as liver disease, pancreatitis, and diabetes mellitus. A recent large survey of Japanese alcoholic men demonstrated that the age-adjusted odds ratio for liver cirrhosis, chronic calcific pancreatitis, and diabetes mellitus was higher in alcoholics with super-active ADH1B or active ALDH2 than in those with less-active ADH1B or inactive ALDH2 (Yokoyama et al. 2013). Moreover, the active form of ALDH2 was associated with hypertension. A meta-analysis of East Asian case-control studies showed the same results; that is, less-active ADH1B and active ALDH2 are associated with a high incidence of liver disease, cirrhosis, and pancreatitis (Li et al. 2011, 2012). This association might be due to differences in alcohol consumption in subjects due to variations in ADH1B and ALDH2.

20.2.5 Clinical Characteristics of Alcoholics with Inactive ALDH2 and Super-Active ADH1B

The variations of ADH1B and ALDH2 have been reported to affect clinical characteristics and the disease course of alcohol dependence. A survey conducted in Japan reported that alcoholic men with inactive ALDH2 developed incidents and symptoms related to alcohol dependence more slowly than alcoholics with active ALDH2 (Murayama et al. 1998). The onset of every symptom was delayed 1–5 years in the inactive ALDH2 group compared with the active ALDH2 group. Interestingly, the onset of alcoholism was earlier in alcoholic women with inactive ALDH2 than those with active ALDH2, which contrasts with the findings seen in male alcoholics (Kimura et al. 2011). One of the reasons for these gender differences might be that the inactive ALDH2 group had psychiatric comorbid diseases more frequently than the active ALDH2 group. In the same way as with ALDH2, the development of alcohol dependence in alcoholic men with super-active ADH1B was delayed compared with those with less-active ADH1B (Eriksson et al. 2001).

There is a difference in personality profile between alcoholics with active and inactive ALDH2. A survey that assessed personality traits using Cloninger's Tridimensional Personality Questionnaire found that alcoholics with inactive ALDH2 revealed higher novelty-seeking and lower harm-avoidance scores compared with those with active ALDH2 (Kimura et al. 2009).

ADH1B polymorphism affects the severity of alcohol withdrawal syndrome. A study using Japanese subjects suggested the prevalence of alcohol withdrawal syndrome was higher in alcoholics with less-active ADH1B than in those with super-active ADH1B (Suwaki et al. 2001). Although there was no difference in alcohol consumption between the super-active and less-active ADH1B groups, the less-active ADH1B group had significantly higher blood alcohol concentrations; therefore, variation in alcohol metabolism may alter the severity of withdrawal symptoms. There is also a report that demonstrates the association between ADH4

polymorphism and the severity of delirium tremens (Gizer et al. 2011). In contrast, there is little evidence of the relation between ALDH2 polymorphism and the severity of alcohol withdrawal syndrome.

20.3 Conclusion

The variations of alcohol-metabolizing enzymes like ADH1B and ALDH2 are strong genetic determinants of drinking behavior and alcohol dependence. Because the polymorphisms of ADH1B and ALDH2 are associated with gastrointestinal tract carcinogenesis, other physical diseases, and clinical alcoholism, a better understanding of these polymorphisms may be useful in the prevention and treatment of alcohol-related problems as well as in the study of the genotypes of alcohol-metabolizing enzymes. One of the mechanisms underlying the effect of the variations of alcohol-metabolizing enzymes is considered to be elevated concentrations of acetaldehyde after drinking. However, many of the mechanisms remain unclear, especially in terms of ADH polymorphisms. Further study is necessary to understand the pathogenesis of alcohol dependence and related disorders.

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Benzodiazepine Abuse and Addiction

21

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Abstract

Chlordiazepoxide's sedative activity was serendipitously discovered by Sternbach in 1955 in Basel, Switzerland, and this first benzodiazepine (BZD) was introduced in 1960 for the treatment of anxiety and insomnia, followed shortly by diazepam in 1963. Given their lower toxicity, BZDs soon replaced barbiturates and other hypnotic drugs, and they became widely prescribed. Although generally considered effective and safe for short-term use for a wide range of conditions, the long-term use of BZDs is much more controversial as they lose efficacy and have been associated with adverse reactions. Problems associated with long-term use include rebound of the symptoms for which they were prescribed, alteration of sleep architecture with loss of sleep efficiency, nightmares, agitation, anterograde amnesia leading to cognitive impairment, confusion, depression, psychomotor compromise with increased risk of falls and motor vehicle accidents, withdrawal symptoms upon discontinuation, and risk of dependence and abuse in special populations. In the late 1980s and early 1990s, a new group of $GABA_A$ receptor agonists at the benzodiazepine receptor site, the Z-drugs, was introduced for the treatment of insomnia, the most common being zaleplon, zolpidem, zopiclone, and its s-enantiomer eszopiclone. Chemically distinct from the benzodiazepine group, they have been promoted to be safer than traditional BZDs and gained wide acceptance with the public and practitioners. However, given their site of action at the benzodiazepine site of the $GABA_AR$, complications are expected to be similar. In fact, the FDA, on May 14, 2013, released a safety announcement recommending a dose reduction for zolpidem extended release as well as a warning not to operate a vehicle or machinery requiring complete mental alertness on the day following the use of zolpidem due to residual psychomotor impairment. Next day sedation, physical dependence and withdrawal, cognitive and psychomotor problems are found in patients receiving Z-drugs. Abuse of the Z-drugs is on the increase and studies suggest that Z-drugs may also increase the risk of depression.

Clinicians prescribing sedatives should ensure short-term use to maximize benefit while minimizing misuse and diversion. They can play a critical role in identifying patients at risk to misuse or divert prescription drugs. Several studies demonstrate that BZD discontinuation in patients with long-term use and dependence is associated with improved quality of life. The management of the patients with BDZ abuse and/or dependence and interventions for BZD detoxification will be described.

21.1 Introduction

Benzodiazepine (BZD) and other BZD receptor agonists (so-called Z-drugs) remain among the most widely prescribed drugs, in spite of recommendations to prescribe SSRIs for long-term treatment of anxiety disorders and melatonin agonists for insomnia. Alprazolam, zolpidem, diazepam, clonazepam, and lorazepam are listed among the 200 most commonly prescribed medications in the United States (Tan et al. 2011). Alprazolam is the tenth most often prescribed medication in the United States, and the number of prescriptions increased from 41.4 million in 2007 to 49.1 million in 2011. Zolpidem follows as the 12th most prescribed drug with 34.5 million prescriptions in 2007 and increasing to 44.6 million prescriptions in 2011. The prevalence of regular BZD use is estimated between 2.2 % and 17.6 % in the general population (Donoghue and Lader 2010; Lader 2011), and 5.4 % of the population receive BZD agonist prescriptions for insomnia.

Public health problems associated with BZDs are mainly due to chronic prescriptions for legitimate symptoms, diversion to other persons than the patients for whom the prescription was initially ordered, and broader illegal trade for nonmedical use. The nonmedical use of prescription drugs has soared in the last 20 years and become a major public health threat. Due to the heterogeneity in individuals classified as "misusers" or "abusers" of prescription medications, it is difficult to determine the true magnitude and clinical significance of problems associated with any particular form of inappropriate medication use (Barrett et al. 2008). However, sedatives are among the medications most frequently used without prescription in the United States (Manchikanti 2006). In one study, 84 % of 3,234 benzodiazepine users identified in a study of 15 general practices were still using them 8 months later, and in the 1996 Australian National Health Survey, 58 % of the 359,300 benzodiazepine users had been taking them for at least 6 months (Parr et al. 2009).

Although misuse and abuse of BZDs can be found at any age, they disproportionately impact vulnerable populations, including the elderly, adolescents and young adults, pregnant women, individuals subject to sexual victimization or dating violence, those with a history of mental illness, and those with a history of substance abuse disorders. BZD misuse is among the most widespread forms of adolescent prescription drug misuse. In population-based national surveys, 9.3 % and 9.5 % of 12th grade students report lifetime sedative and anxiolytic use for recreational purpose (Johnston et al. 2009). In European countries, an average of 5.6 % of adolescents had used tranquilizers/sedatives with prevalences ranging from 1.5 % in Ukraine and the United Kingdom to about 13 % in Lithuania and France. In Brazil, adolescents have a 5 % lifetime use of sedatives or tranquilizers; females and students attending private schools are at increased risks of BZD use (Opaleye et al. 2013).

Long-term use of BZDs is prevalent among seniors in North America, Australia, and Europe (Curran et al. 2003). Approximately 9–54 % of elderly adults have used benzodiazepines in a given year (Llorente et al. 2000), and two thirds of the prescriptions were inappropriate.

People who are mentally or physically vulnerable are more likely to misuse these drugs. In 2009, at least 33 % of drug-related emergency department (ED) visits in

the United States were related to CNS depressants. ED visits involving benzodiazepines more than doubled between 2004 and 2009. This demonstrates an alarming increase in the abuse of BZDs and other non-BZD hypnotics. In addition, there is a significant increase in the involvement of alprazolam, clonazepam, and zolpidem in drug-related suicide cases since 2004, with a 148 % increase for zolpidem and a 105 % increase for alprazolam.

Substance abuse treatment programs and emergency departments' data indicate that the combination of benzodiazepines and narcotic pain reliever abuse is common as 80 % of people who abused benzodiazepines also misused other drugs, most commonly opioids. An estimated 3–41 % of alcoholics abused benzodiazepines. The rehabilitation of patients who also abuse BZDs in combination to other drugs is very challenging as they represent a treatment-resistant population.

The number of admissions to addiction treatment for abuse of BZDs nearly tripled in the United States between 1998 and 2008, compared to an 11 % increase in overall substance abuse admissions. The number of annual admissions for combined abuse of benzodiazepine and narcotic pain reliever increased by 570 % from 5,032 admissions in 2000 to 33,701 admissions in 2010. The majority of these admissions were non-Hispanic white males between 18 and 34 years of age. Most BZD abusers (95 %) reported abuse of another substance besides the BZD, with 82.1 % reporting primary abuse of another substance and 12.9 % reporting primary abuse of BZD (SAHMSA Treatment Episode Data Set 2011).

21.2 Pharmacology of Benzodiazepine and Other BZD-Site Agonists

BZDs and the Z-drugs are allosteric modulators on the gamma-aminobutyric A receptor ($GABA_AR$). Gamma-aminobutyric acid (GABA) is the most important inhibitory-type neurotransmitter and its actions are mediated by ionotropic ($GABA_A$)- and metabotropic ($GABA_B$)-type receptors, which are widely distributed throughout the central nervous system. The $GABA_AR$ are ligand-gated ion channels allowing influx of chloride (Cl-), causing hyperpolarization of the neuronal membrane, and inhibiting the firing of new action potentials. The $GABA_AR$ is a transmembrane receptor made of five subunits (2 α, 2 β, and 1 γ) binding GABA on the extracellular side of the receptor. It takes two GABA molecules to activate $GABA_AR$. Barbiturates bind between the γ and β_2 subunit, while BZD and the Z-drugs bind between α_1 and $\gamma 2$ interface. Barbiturates, benzodiazepines, and ethanol are $GABA_A$-positive allosteric modulators (i.e., their binding induces a neuronal response only in the presence of the actual agonist GABA), with two GABA molecules needed to open the chloride channel. BZDs and Z-drugs act as GABA potentiators by increasing the frequency with which the chlorine channel opens when two GABA molecules bind to $GABA_AR$. The increase in intracellular chloride concentration hyperpolarizes the neuron which becomes less excitable (Heikkinen et al. 2009; Tan et al. 2010).

It is through their ability to increase the potency of $GABA_AR$ that BZDs and Z-drugs produce a transient relaxation for patients with anxiety or insomnia disorders.

The shorter the onset of action after drug taking, the more efficient is the learning of the subjective effect associated to the drug. With BZDs of short onset of action (30 min), the individual learns that relaxation, stress relief, or sleep is obtained by taking a pill rather than by learning more effective practices of stress reduction and a more structured lifestyle with regular sleep hygiene. Moreover, attempts to discontinue medications after several weeks of regular intake are met with resurgence or rebound of the primary symptom of anxiety or insomnia, frustrating the attempts, triggering further drug seeking, and leading to automatic and compulsive drug-taking behaviors or the cycle of addiction. With chronic intake, tolerance sets in to the effect and duration of the desired effect of the drug, requiring increases in doses and frequency of doses. Tolerance to chronic benzodiazepine use appears to result from neuroadaptive processes involving both desensitization of inhibitory gamma-aminobutyric acid (GABA) receptors and sensitization of excitatory glutaminergic receptors (Ashton 2005).

When high-dose benzodiazepines or ethanol is abruptly discontinued, this "downregulated" state of inhibitory transmission is unmasked, leading to characteristic withdrawal symptoms of anxiety, insomnia, irritability, autonomic hyperactivity, sweats, and, possibly, seizures.

Benzodiazepine drugs form a homogenous class of medications made of a benzene ring and a diazepine ring. The differences between the different benzodiazepine drugs are in their side chains. On the other hand, the non-benzodiazepine drugs (Z-drugs) bind specifically to and activate the benzodiazepine site of $GABA_A$ receptors but they are not chemically related to benzodiazepines. They are principally classified into three groups of chemicals: (1) imidazopyridines (zolpidem, alpidem, necopidem, saripidem), (2) pyrazolopyrimidines (zaleplon, divaplon, fasplon, indiplon, loredipIon, ociplon, panadiplon, taniplon), and (3) cyclopyrrolones (eszopiclone, zopiclone, pagoclone, pazinaclone, suproclone, suriclone). Given their specific binding and allosteric modulation of $GABA_A$, these drugs have similar long-term negative effects to benzodiazepines including adverse cognitive (amnesia) and psychomotor effects, compromise in balance, standing steadiness, night falls, and motor incoordination leading to driving impairments. Due to their heterogeneous chemical classes, routine toxicology screens for drugs of abuse do not include the Z-drugs sedatives, so that the extent of their impact on emergency room visits and other societal costs remain underreported. In clinical trials, these sedative hypnotics were found to more than double the risk of depression compared to the groups taking placebo. Consequently, the long-term use of sedative hypnotic drugs increase the suicide risk as well as overall mortality risk (partially due to increase in risks of cancer and infections). The Z-drugs have similar risks of rebound and withdrawal effects as benzodiazepine drugs.

21.3 Clinical Uses of BZDs and Z-Drugs

In this section, we are first reviewing accepted indications for BZDs. BZDs and other BZD-site agonists are indicated for short-term use and at the lowest effective dose for these indications.

Indications include panic disorders and phobias preventing specific functions or procedures (such as flying in an airplane, undergoing an MRI for patients with claustrophobia). They are also indicated for short-term management of anxiety disorders, such as caused by a sudden stressor such as grief, and the short-term management of insomnia associated with alcohol withdrawal, withdrawal from sedatives with short half-lives, emergency intervention for grand mal seizures, and muscle relaxant of severe muscle spasms. They are used in the treatment of acute paranoia or other psychotic state induced by cocaine or other drug toxicity, in short-term intervention of psychiatric emergencies accompanied by psychosis or mania, and to induce sedation before the onset of action of lithium or other antipsychotic medications (neuroleptics). They are also used for premedication to relieve anxiety of an upcoming surgical procedure or dental intervention, in anesthesia induction, sedation for procedural medical interventions, and sedation in intensive care (to facilitate mechanical ventilation and/or sedate patients in distress).

21.4 Pharmacokinetic

BZDs are well absorbed by the gastrointestinal tract after oral administration. After intravenous administration, BZDs quickly distribute to the brain and central nervous system. Only midazolam has reliable absorption after intramuscular administration. The main difference between BZDs relates to the time to peak effect (onset of action) and duration of action, depending on the metabolic half-life and the presence or not of psychoactive metabolites. BZD characteristics predicting the severity of the benzodiazepine withdrawal syndrome are higher dose, longer duration of treatment, shorter half-life, and more rapid taper. Clinical variables of BZD withdrawal severity include severity of preexisting anxiety and/or depression, personality disorder, panic disorder, and history of or concurrent substance use disorder. Withdrawal from rapidly absorbed, short-acting drugs with no active metabolites (e.g., alprazolam, triazolam) can start within hours of the last dose; withdrawal from substances with long-acting metabolites (e.g., diazepam) may have gradual onset with a peak within 1–10 days after the last dose.

21.5 Problems Related to the Long-Term Use of BZDs

The long-term clinical use of BZDs is much more controversial. Advocates of long-term management with BZDs quote patients' acceptability and widespread belief of safety and efficacy. However, several academic and public health policies strongly advise against long-term use of BZDs for PTSD, generalized anxiety, insomnia, depression, and panic attacks due to the lack of evidence of demonstrated long-term efficacy in the treatment of these conditions and their problematic effects (Table 21.1).

Sedatives adversely affect cognitive (memory, attention) and psychomotor functioning impacting daily activities. BZD-associated impairments in reaction time,

Table 21.1 Potential problems related with the use of BZDS

Potential side-effects of BZDs
Sedation, residual effects during day-time
Cognitive effects, especially in mild cognitive impairment
Amnesia, not remembering activities
Impulsivity associated with poor working memory
Impairment – implications while driving, operating machinery
Potentiation of respiratory depression from other medications (opioids)
Paradoxical reaction due to desinhibition
Reinforcement of avoidance, inflexibility: prevents coping/learning of adaptive response
Problems associated with long-term use of BZDs or Z-drugs
Impairment, psychomotor deficits (cerebellar: unsteadiness, nystagmus, propensity to falls, poor coordination, slurred speech, disorientation). Increase risk of falls with injuries in elderly (falls at night with head injuries, hip fractures, etc.)
Decrease in self-regulation and awareness (metacognition): decrease in ability to perform simple repetitive tasks (decrease in skills, including driving skills), increase in reaction time, decrease in accuracy of performance, decrease in performance in tasks of attention
Decrease in cognition: decrease in memory consolidation and learning (anterograde amnesia). The memory impairment increases with tasks of increased complexity
Acceleration of cognitive decline in elderly or potential for pseudodementia in elderly or other vulnerable patients. Cognitive failures
Increase in the risk of motor vehicle accidents (60–80 % more accidents in drivers on BZDs or Z-drugs)
Behavioral problems with forensic implications. Problems of disinhibition in persons with borderline personality disorders or impulse disorders. This can lead to paradoxical increase in anxiety, hyperactivity, and aggressive impulses. The person may not have any recollection of the incident (fugue states)

attention, and visuospatial skills increase vulnerability for motor vehicle accidents. There is also a clear association between the use of BZDs in aged people and increased risk of falls and fractures and of traffic accidents (Thomas 1998; Gunja 2013). Psychomotor impairment, falls, and hip fractures are more likely to occur with Z-drugs that have longer half-lives.

Among war veterans, potential adverse consequences are BZD misuse and/or addiction, especially among those patients with an already established substance use disorder. Disinhibition has been described in patients with traumatic brain injury; these two conditions are common and often underdiagnosed among veterans with PTSD returning from Iraq and Afghanistan. In addition, it is becoming apparent that BZDs have the potential to reduce the effectiveness of exposure-based psychotherapy, which is considered a pillar in the treatment of veterans with PTSD and requires effective short-term memory, as the mechanism underlying effectiveness is a change in memory (Lund et al. 2013).

Evidence-based guidelines insist on BZD's liability for physical dependence which may occur even with appropriate therapeutic dose but for longer period of time. The risk for negative effects such as abuse and dependence is minimized when they are prescribed for short term (e.g., 2–4 weeks for intense grief reaction).

As stated earlier, because of rebound, i.e., exacerbation of symptoms for which the medications were taken initially, a large proportion of BZD recipients become chronic users, with ensuing development of tolerance and the potential for physical and psychological dependence. The dilemma is the difficulty to prevent what is anticipated for short-term therapy to become long-term misuse with no established evidence of long-term benefit and the liability of dependence and negative psychomotor and cognitive side effects (Lader 2011).

21.6 BZDs Misuse, Abuse, and Dependence

Three different populations of patients with BZD dependence can be described (Lader 2011), and this classification is useful to guide the type of intervention:

- Those who are prescribed benzodiazepine at constant dose for more than 3 months, i.e., they are at risk of negative cognitive consequences from BZDs. These may include patients on multiple psychoactive prescription medications for chronic pains (iatrogenic dependence).
- Those who are prescribed BZDs for more than 3 months and are progressively increasing their doses.
- Those who use BZDs both from legal and illegal sources in a pattern reminiscent of polysubstance abuse.

Many people who take prescription sedatives take them responsibly and benefit from their use, especially if they are taken for short term (less than 6 weeks). Longer duration or high dose of benzodiazepine use, however, increases the odds for developing benzodiazepine dependence (Kan et al. 2004). Also, women and those who have preexisting cognitive impairment (elderly), panic disorders, or suicidal ideations have elevated odds of developing dependence on benzodiazepines (Voyer et al. 2009). If BZD doses are voluntarily or involuntarily reduced or stopped, withdrawal symptoms or resurgence of the initial symptom is likely to occur. This type of physiological dependence is the most common and it is believed that several millions worldwide have this type of BZD dependence.

21.7 Recreational BZD Abuse

Intentional abusers actively seek the sedatives because of their rewarding psychoactive properties. Sedatives can be abused due to their ability to relax anxious feelings and remove inhibitions (such as during social encounters), similar to the euphoric feelings induced by alcohol or illegal drugs (Yu 2012).

The drugs are purchased from legal or illegal sources for recreational use or obtained from friends or family members who have prescriptions. Other sources include illicit sales of diverted supplies or the Internet. The modern everywhere technology, such as the easy access to Internet, plays a significant role in this regard by opening up a new source for access to drugs, explaining a portion of the increase in their abuse. Illegal online pharmacies sell controlled substances, including

sedatives, over the Internet without regard for local laws, without a valid prescription, and without medical guidance and supervision (Forman et al. 2006). Direct marketing of medications to patients through media (especially television) may be related to changed attitudes toward ingestion of psychotherapeutic agents.

Misuse of psychoactive medications, particularly in the case of individuals with prescribed BZDs, may not only stem from the individual factors but from a lack of quality health-care service. The fact that these drugs are considered "medication" and are endorsed by physicians may give a false sense of safety. Health-care providers may inadvertently play a role in misuse behaviors by failing to recognize a patient's potential for developing a substance abuse/dependence disorder, misdiagnosing the patient, overprescribing the medication, or just due to time pressure on the physician: it takes more time to refuse a patient's request and teach alternative behavioral strategies for anxiety or insomnia than to agree and write the requested prescription.

Increased "medicalization" and pharmacotherapeutic management of common symptoms such as insomnia and subsequent increase in prescription of BZDs or Z-drugs have also led to more addiction and abuse problems. More worrisome, and by no means rare, are those who are on chronic prescription of opiates and sedatives for chronic pain, given the increased potential for respiratory depression and cardiac arrest especially with comorbid diagnoses of COPD or obstructive sleep apnea.

Finally, while doctor shoppers, physicians, and the Internet receive much of the attention regarding diversion, data suggest that there are numerous active street markets involving patients, Medicaid recipients, and pharmacies as well. Diversion can occur in many ways, including the illegal sale of prescriptions by physicians and those who are referred to on the street as "loose" pharmacists; "doctor shopping" by individuals who visit numerous physicians to obtain multiple prescriptions; theft, forgery, or alteration of prescriptions by health-care workers and patients; robberies and thefts from manufacturers, distributors, and pharmacies; and thefts of institutional drug supplies. Many of these individuals have conditions that have been appropriately diagnosed and addressed with a proper course of treatment but are selling their prescription drugs for profit or exchanging them for illicit drugs. In addition, there are many individuals posing as legitimate patients for the purposes of scamming physicians and pharmacists or otherwise defrauding the system (Inciardi et al. 2007).

21.8 BZD Withdrawal Syndrome

Withdrawal symptoms can sometimes occur after as little as 4 weeks of daily use of BZDs but occur in about half of the patients treated daily for more than 4 months (el-Guebaly et al. 2010), and may last for 6–8 weeks. In some protracted cases, it can last for months. However, many patients will report more restorative sleep and improved quality of life after a few weeks off the medications, due to improved cognitive and psychomotor functioning (Salzman et al. 1992).

The onset of withdrawal symptoms produces subjective "need" for BZDs (or craving) prolonging their use, often for years after the initial indication for the drug has passed. Many long-term users, aware that the drugs are no longer effective and are causing adverse effects, try to stop but are unsuccessful because of the emergence of withdrawal symptoms (Ashton 2005).

The symptoms after discontinuation of BZDs have been described in different ways:

Recurrence or relapse refers to reemergence of symptoms that existed prior to the treatment but at the same intensity.

Rebound refers to symptoms similar to the symptoms the patient had before using BZDs but experienced with increased intensity.

Withdrawal refers to a cluster of symptomatology due to autonomic hyperactivity. This is believed to be a hyperexcitability in the same physiological system that was initially modified by the drug, which meant to counteract the effects of the drug in an attempt to maintain homeostasis.

As stated before, the symptoms of BZD withdrawal are a function of their pharmacokinetics, duration of use, the underlying diagnoses, or individual personality. Withdrawal symptoms include anxiety; irritability; agitation; tremulousness; increased sensory perception such as photophobia, hyperosmia, or altered taste; hyperacusis; paresthesia; and hypersensitivity to touch. Patients also can have allodynia, pain, sore eyes, myalgia, insomnia, fatigue, lethargy, lightheadedness, dizziness, tinnitus, depersonalization, derealization, poor concentration, poor memory, headaches, depressed mood, palpitations, nightmares, diaphoresis, muscle twitching, muscle ache, memory and concentration impairments, dizziness, feeling faint, and gastrointestinal symptoms such as anorexia and nausea (Peturson 1994). Occasionally, more severe symptoms such as seizures, psychotic reactions, or delirium and rarely death from complication of seizure can occur. Kindling is a neurologic sensitization phenomenon resulting from repeated sedative withdrawal episodes and leading to more severe withdrawal intensity upon successive episodes, including an increased propensity to seizures.

21.9 BZD Abuse in Specific Populations

While in the past sedative medications traditionally have been prescribed to women and older age groups, the growing problem of prescription drug abuse in the beginning of the twenty-first century affects individuals of both genders and of all ages, including middle school-aged children (ages 12–16) worldwide. For example, in Canada, a national health survey showed the use of sedatives doubled between 1994 and 2003 with particular increase among men, individuals under 60 years of age, and among obese men and underweight women (Vozoris and Leung 2011). Usually, high prevalences among specific populations reflect the presence of underlying conditions that can explain in part the known relationship between sedatives and morbidity/mortality. This is the case of the greater odds of sedative medication use found among morbidly obese men complicating obesity-related

sleep disruption (obstructive sleep apnea) and the associated cardiac mortality risk that has been found to be increased in the presence of BZDs. The same is true with chronic obstructive pulmonary disease, when the anxiety triggered by shortness of breath is treated with BZDs.

21.10 Adolescents and Young Adults

The lifetime prevalence of anxiety ranges between 15 % and 20 % and the median age of onset is 11 years of age, constituting one of the most common and earliest type of psychopathology among children and adolescents (Mohr and Schneider 2013). Anxiety disorders are found in 5–19 % of all children and adolescents, and in children younger than 12, prevalence ranges between 2.6 % and 5.2 %, with separation anxiety as the most common disorder (Costello et al. 2004; Ford et al. 2003). Children with an anxiety disorder are more likely to be engaged in drug abuse activities as young adults at follow-up (Beesdo et al. 2009).

Sleep disorders are also very common in pediatric populations, with as many as 17 % of adolescents having unrestorative sleep (Roberts et al. 2002). However, sleep problems among children often go unrecognized in general practice, in part because of parents underreporting of sleep problems in their children or adolescents. Awareness of the importance and potential consequences of sleep problems on academic performance, neurocognitive function, and daytime behavioral problems has to be emphasized (Blunden et al. 2004). Children and adolescents are frequently sleeping less than 9 hours at night, the recognized minimum amount of sleep required in this age group. Intrinsic contributors to inadequate sleep patterns in children and adolescents include developmental changes causing a shift in circadian rhythm during puberty, delayed sleep phase syndrome (7 % of adolescents), sleep-disordered breathing, and insomnia-type symptoms found in up to 34 % of adolescents. Extrinsic factors include early school start time and poor sleep habits (also called sleep hygiene) such as use of electronic devices near or during bedtime and caffeine consumption, especially problematic when undisclosed in soda or other foods (Tan et al. 2012). Anxiety, poor academic performance, behavioral problems, and sleep problems have been recognized as risk factors for substance use, abuse, and dependence.

The nonprescribed use of sedatives among adolescents and young adults is a cause of concern in many countries. Fast brain development during this life stage, especially the development of executive function and learning acquisition, implies that exposure to amnesia-inducing drugs may stunt development and result in devastating neurobiological changes and behavioral consequences such as missed educational milestones, increased impulsivity (inversely correlated with short-term memory), and school dropouts. Young people report using sedatives to relieve anxiety symptoms and to sleep, with high percentage of teenagers and many of their parents believing that prescription drugs, even taken nonmedically, are more safe than illegal drugs.

Uncharted societal changes exposing children and adolescents are increased exposure to direct-to-consumer advertisement of medications since 1992, rushed medical visits promoting fixing of problems via prescription while decreasing

patient–clinician interaction, increased media distractions, and increased time competition for numerous activities all potentially resulting in increased anxiety.

21.11 Elderly

Published guidelines advise against the use of benzodiazepines or Z-hypnotics (BZD-Z) in the elder. However, inappropriate use of BZDs and non-BZDs among this age group is widespread although the risk–benefit ratio is clearly greater than 1. Estimated prevalence rates of insomnia in older people is over 30 %, and studies report that a third to half of seniors in North America and the United Kingdom are prescribed either a Z-drug or benzodiazepine for sleep disturbance (Glass et al. 2005; Nubukpo and Clement 2013). These are concerning statistics given the risks of sedatives in this age group for adverse health consequences. Older adults experience high rates of illnesses and are exposed to numerous pharmacologic agents, decreased drug metabolism, and increased susceptibility to toxic effects and cognitive and motor impairment, including falls and injuries. These medications can interact with over-the-counter medicines and dietary supplements, consumed in significant quantities by seniors. Cognitive adverse events (memory loss, confusion, disorientation, pesudodementia), psychomotor-type adverse events (reports of dizziness, loss of balance, or falls), and morning impairment (residual morning sedation) can lead to accidents, including when operating vehicles. Patients over 65 are significantly less likely to stop BZDs than younger patients (Holden et al. 1994); however, drug dependence is often unrecognized among older adults.

21.12 Women

Women are a vulnerable population for BZD drug abuse. First, women are more likely than men to suffer from depression, anxiety, trauma, and victimization, all of which are also associated with substance abuse. Second, women at different ages report using drugs to cope with stressful situations in their lives. Third, studies suggest that women are significantly more likely than men to be prescribed medications with high abuse liability such as narcotics and anxiolytics and not rarely in combination and for long periods of time.

BZDs cross the placenta and have the potential to accumulate in the embryo/fetus and may consequently cause adverse problems (Iqbal et al. 2002). The general consensus is that BZDs have low teratogenic potential but may be associated with an increased risk of cleft palate. Current recommendations are that in order to minimize risk if BZDs are absolutely needed, they should be prescribed at the lowest effective dose for the shortest possible duration, avoiding use in the first trimester and avoiding poly-pharmacotherapy use (Dell'osso and Lader 2013). Pregnant women on BZDs are often tapered off their BZD treatment. However, there is a portion of BZD-dependent pregnant women who are unable to discontinue their BZDs in spite of knowing the associated risk of cleft palate and the potential harm of BZD on the developing brain.

Pregnant women substance users with BZD dependence are in general very impaired, emotionally challenged with frequent relapses and issues of noncompliance with treatment recommendations possibly due to underlying trust issues. BZDs should never be used for pregnant women with other addictive disorders as they increase impulsivity and prevent learning more adaptive coping skills. Moreover, when BZDs are continued into the late pregnancy, neonatal abstinence syndrome may occur in the baby and can be prolonged. This additional stressor at the start of life is not only detrimental to the baby, as her irritability may jeopardize bonding between the mother and child dyad, which may be very significant given the preexisting vulnerabilities of the mother. Alternative approaches to treating anxiety and stress during pregnancy are "desperately" needed, and more should be done to validate the usefulness of integrative approaches to improve self-regulation during pregnancy.

21.13 Polysubstance Users

The prevalence of benzodiazepine abuse reaches up to 50 % among opiate-dependent individuals, including those on agonist maintenance treatment. BZD use in opioid-dependent populations is a predictor of overdose, lethality, and poor treatment outcome including cocaine and other drug use, self-harm behaviors, and poor psychosocial functioning. Methadone fatalities include benzodiazepines in 75 % of cases as do almost all buprenorphine fatalities.

Benzodiazepines are frequently abused in combination with alcohol or other drugs (mainly opiates) to enhance the subjective reward of the primary substance, to offset their adverse effects (e.g., irritability induced by stimulants), or to alleviate withdrawal symptoms including insomnia due to a relative lack of access to the primary substance such as alcohol or opiates. The abuse of benzodiazepines in combination with other central nervous system depressants is particularly dangerous due to potentially fatal respiratory depression.

The rehabilitation literature demonstrates that among illegal drug users, those who also abuse benzodiazepine have worse outcome. This phenomenon could have several explanations: the concurrent dependence on BZDs and opioid pain relievers could lead to more severe withdrawal symptoms than opioid withdrawal alone, resulting in higher treatment attrition rates. More anxious patients are more averse or avoidant of discomfort and resistant to alternative treatment modalities (BZDs decrease flexibility). The negative impact of BZDs on memory and cognition prevents learning coping strategies indispensible to achieve abstinence.

21.14 Drug-Facilitated Rape

Ingestion of intoxicant during parties puts participants at risk for sexual assaults. Studies on the prevalence of drug-facilitated sexual assaults have been conducted in the United States. Of 1,179 urine samples from victims of sexual assault analyzed

over a 29-month period, alcohol was found in 41 %, followed by cannabinoids in 18.5 %, benzodiazepines in 8 %, and benzoylecgonine (cocaine metabolite) in 8 % (ElSohly and Salamone 1999).

A special case of BZD abuse is the surreptitious BZD administration to an unsuspecting victim by sexual predators. In addition to alcohol, the so-called date rape drugs most frequently used by rapists to sedate their victims are flunitrazepam (Rohypnol®), a fast-acting benzodiazepine, ketamine, and gamma hydroxybutyrate (GHB) and its congeners. Perpetrators choose these drugs because they act rapidly, produce disinhibition and relaxation of voluntary muscles, and cause the victim to have lasting anterograde amnesia for events that occurred under the influence of the drug. Many drugs associated with rape are given via alcohol, and alcoholic beverages potentiate the drug effects.

21.15 Treatment of BZD Dependence

The management of patients with BZD dependence includes three concurrent aspects: management of the acute withdrawal phase (Voshaar et al. 2006), developing strategies for addressing the underlying condition, as well as crisis management. Clinicians need to work closely with patients showing empathy in helping manage distress while providing menus of integrative or supportive therapies from which patients can choose from. Educational materials and tips regarding insomnia (sleep hygiene, sleep diary) and anxiety (cognitive behavioral programs, self-help materials, referrals to mindfulness resources, bibliographies) should be provided.

21.16 BZD Detoxification

For some long-term BZD user patients, minimal interventions such as brief consultation or a letter with information about risks of long-term use of BZDs and the recommendation for their discontinuation can be effective and do not produce adverse effects (Cormack et al. 1994; Heather et al. 2004).

The management of BZD withdrawal syndrome includes, either independently or in combination, (1) gradual tapering of the BZD, (2) switching to an equivalent dose of a long half-life BZD before gradual tapering of the latter (Lader et al. 2009), (3) the use of adjuvant medications, (4) treatment of the underlying conditions (i.e., SSRIs for anxiety) prior to detoxification and continuing these medications after BZD discontinuation (Rickels et al. 1990), and (5) non-pharmacologic treatments of underlying conditions (Table 21.4).

21.16.1 Gradual Tapering of the BZDs

The rate of BZD taper is different for each patient and needs to be individualized, but there are some common recommendations depending on the type of BZD

Table 21.2 Benzodiazepines in equivalent doses of diazepam* and half-life elimination

Benzodiazepine	Equivalent dosage (mg) of *diazepam 10 mg is approximately equivalent to	Half-life elimination (h)
Alprazolam	0.5 mg	6–12
Chlordiazepoxide	25 mg	5–30
Clonazepam	0.5 mg	18–50
Diazepam	10 mg	20–100
Flunitrazepam	1 mg	18–26
Flurazepam	15–30	25–100
Loprazolam	1 mg	6–12
Lorazepam	1 mg	10–20
Lormetazepam	1 mg	10–12
Nitrazepam	10 mg	15–38
Oxazepam	20 mg	4–15
Temazepam	20 mg	8–22

Table 21.3 Z-drugs in equivalent doses of diazepam* and half-life elimination

Z-drugs	Equivalent dosage (mg) of *diazepam 5 mg is approximately equivalent to	Half-life elimination (h)
Zaleplon	10 mg	1–2
Zolpidem	10 mg	2–4
Zopiclone	7.5 mg	4–8
Eszopiclone		4–8

pattern of use/misuse/dependence. A common recommendation is a reduction by 10–15 % every 1–2 weeks, leaving some empowerment to the patient for decision-making. Individualizing treatment seems to result in better treatment retention. There is evidence that most patients will be able to complete taper in 6–8 weeks, although some patients may need more time, including up to a year (Ashton 2005).

21.16.2 Switching to an Equivalent Dose of a Long Half-Life BZD Before Tapering Withdrawal

For patients dependent on the more potent BZDs (lorazepam, clonazepam) or on those with short duration of action (alprazolam, triazolam, zaleplon, zolpidem), it is recommended to switch to a diazepam equivalent for a few days and then rapidly taper off diazepam. This ensures a smoother detoxification as the drug will continue to taper itself for another 3–4 weeks after it is discontinued (Tables 21.2 and 21.3). Dose equivalence to diazepam can also be found at http://www.benzo.org.uk/bzequiv.htm.

For heavy BZD-dependent polysubstance abusers, outpatient detoxification may have less chance of success due to the availability of BZD from illegal sources, and residential treatment may be necessary to complete the detoxification after

diazepam substitution and taper over 2–3 weeks. Especially in this group, the use of adjuvant antiepileptic medications is indicated (see below).

21.16.3 Adjuvant Medication Treatment to Decrease BZD Withdrawal Symptoms

Antiepileptic medications such as carbamazepine, its safer metabolite oxcarbazepine (Croissant et al. 2008), and valproic acid are useful adjunct medications for attenuating BZD withdrawal symptoms especially for those coming off higher BZD doses, such as more than 20 mg diazepam equivalent daily. The newer antiepileptic zonisamide, which acts as both GABA enhancer and glutamate inhibitor, should also be investigated as it was found superior to diazepam on symptoms of craving, withdrawal, and depression for alcohol withdrawal (Rubio et al. 2010). Other GABA medications have been evaluated for BZD detoxification such as pregabalin (Bobes et al. 2012) and gabapentin. However, all these antiepileptic medications should not be considered for long-term substitution to BZD because of their negative effects on cognition.

Propranolol, captodiamine, and buspirone were not found to be effective in facilitating BZD withdrawal. Inpatient detoxification with the BZD antagonist flumazenil has been described, although patients in this study were then switched to and discharged on the long-acting BZD clonazepam at high doses (2–6 mg), so that the procedure cannot be considered a detoxification from BZD although the authors report that 53 % of their patients were BZD-free at 6 months (Quaglio et al. 2012). A double-blind evaluation of the procedure without substitution with a BZD, possibly under the protective effect of a non-BZD antiepileptic medication, has to be undertaken before the procedure can be recommended. The use of flumazenil in the setting of BZD dependence should be advocated with caution due to the high risk of seizures and aspiration.

21.16.4 Pharmacologic Treatment of Underlying Conditions

It is important to treat any underlying condition before, during, and after BZD withdrawal treatment. SSRIs and other antidepressant with low stimulating potential (sertraline, paroxetine, citalopram, escitalopram, mirtazapine, trazodone) are recommended for anxiety disorders, especially with concurrent depressive symptoms. Melatonin is recommended for insomnia.

21.16.5 Non-pharmacologic Treatment of BZD Addiction

Maximizing the use of non-pharmacologic interventions is critically important, and different types of health-care providers can play a significant role in providing these psychosocial interventions. We are briefly reviewing non-pharmacologic

Table 21.4 Steps recommended for BDZ discontinuation after long-term use

1. Send a letter or have a conversation with the patient explaining the negative consequences of long-term use of BDZs. Explain the process of taper and the non-pharmacologic options to deal with the symptoms related to BDZ discontinuation and/or underlying problems
2. Change to longer-acting medication and taper over a period of 6–12 weeks
3. If step 2 fails or the patient has a severe dependence with risk of seizures, use a medication to suppress the withdrawal symptoms for several weeks before and after BDZ reduction
4. If step 3 fails or the patient is at risk for complications, use inpatient dose reduction of BDZ over a period of 1–3 weeks
5. Consider the need for psychiatric or hypnotic medication different than BDZ to treat underlying anxiety and/or insomnia
6. Refer for therapy (CBT, mindfulness-based therapy, support groups)

approaches to the treatment of anxiety and sleep disorders. Although the review of these strategies is beyond the scope of this chapter, clinicians will benefit their patients in developing familiarity with self-empowering strategies aimed at improving quality of life and health by reducing stress while minimizing risks associated with pharmacologic management.

Historically, psychotherapy for anxiety disorders (panic, generalized anxiety, social anxiety, phobias) was the first available treatment to provide relief for anxiety symptoms. The initial long-term dynamic therapy has been replaced by short-term intensive dynamic psychotherapy, cognitive behavioral therapy, and other interventions such as exposure therapy and mindfulness-based therapies.

There are several promising therapies that have been used recently to treat anxiety. Some of them are COPE (Creating Opportunities for Personal Empowerment) that is a brief-focused cognitive behavioral therapy-based intervention that can be delivered to teens in school settings using a group format. Adolescents who received this therapy reported significant decreases in depression and anxiety on the Beck Youth Inventory as well as increases in personal beliefs about managing negative emotions. Evaluations indicated that the group COPE intervention was a positive experience for the teens (Mazurek Melnyk et al. 2013) (Table 21.4).

A 12-session program of mindfulness-based stress reduction (MBSR) in seventh and eighth graders at a small school for low-income urban boys resulted in less anxiety, improved coping, and a possible attenuation of cortisol response to academic stress, when compared with Health Education participants (Sibinga et al. 2013).

Pathological worry is considered a central symptom of generalized anxiety disorder but can be seen in other types of anxiety (e.g., excessive worry over future panic attacks). For that reason, studies of interventions that reduce pathological worry are considered very important. Results from a meta-analysis performed by Covin et al. (2008) found that cognitive behavioral therapy (CBT) for GAD can be a highly effective treatment for reducing pathological worry, especially for younger adults. CBT was also effective for geriatric patients and the improvement was both for the short term and over time.

Avoidance is another cardinal feature in patients with anxiety disorders and is a maladaptive learned behavior that may temporarily relieve anxiety symptoms but actually perpetuates the anxiety often causing significant impairments in functioning. Avoidance of the uncomfortable symptoms of the withdrawal or rebound reactions during BZD tapering is a major difficulty in interrupting the vicious cycle of using BZDs to combat painful subjective states during the recovery from BZD misuse and dependence. To break this cycle, it is essential for individuals with co-occurring disorders to learn strategies to self-regulate anxiety symptoms as well as alternative coping strategies. The psychological support is required during and after the withdrawal because patients remain extremely vulnerable for several months after discontinuation. Cognitive behavioral therapies (CBTs) are among the most efficacious psychosocial treatments that can be used to treat individuals with anxiety disorders and SUDs. Action commitment therapy (ACT, Blackledge and Hayes 2001) has also found wide acceptance as effective treatment for avoidance and anxiety disorders.

CBT demonstrated efficacy in SUD across diverse populations (Carroll and Schottenfeld 1997). The CB model of relapse is based on linear progression of responses in high-risk situations. It believes that increase in self-efficacy leads to increased coping with anxiety and stress and less substance use. Combination of CBT with contingency management and relapse prevention combined with pharmacotherapy are among the most successful treatments (Epstein et al. 2003). Acceptance commitment therapy (Blackledge and Hayes 2001) is a third-wave cognitive behavioral therapy intervention focusing on methods such as acceptance, mindfulness, cognitive defusion, decentering, and metaphors meant to reduce the impact of negative thoughts and feelings.

Although prolonged exposure therapy (Foa et al. 2007) has been deemed one of the treatments of choice for PTSD, there is limited research exploring its efficacy in substance-abusing populations because of the fear that exposure to trauma cues would precipitate relapse. Physical exercise may enhance sleep and contribute to an increased quality of life in older adults (Montgomery and Dennis 2002), and increased physical activity is favorably associated with restoring sleep (Lang et al. 2013). Cognitive behavioral therapy for insomnia is as effective for improving sleep quality while decreasing depression and improving mental health.

21.17 Prevention of BZD Abuse

21.17.1 Awareness of Professional Guidelines

Countries have created guidelines aiming at reducing the chronic use of BZD and consequently the risks of misuse and abuse. Several academic (American Psychiatric Association (APA), the National Institute for Health and Care Excellence (NICE), Royal Australian and New Zealand College of Psychiatrists (RANZCP), the UK Committee on Safety of Medicines (1988)) and governmental agencies (U.S. Department of Veterans Affairs (VA) and the U.S. Department of Defense (DoD),

the UK Department of Health via the Chief Medical Officer (2004)) have created evidence-based guidelines describing indications and recommended length of time for BZD use. Most of these guidelines emphasize selective serotonin reuptake inhibitors (SSRI) as first-line treatment for generalized anxiety, panic attacks, and post-traumatic stress disorder and generally discourage the use of BZDs. However, primary and mental health-care providers frequently continue prescribing BZDs in situations not included in the guidelines (Abrams et al. 2013).

21.17.2 Screening

Due to the strong association between anxiety disorders and substance use, as well as the strong association between drug abuse and prescription drug misuse, it is imperative to include screening questions regarding alcohol, smoking, and substance use histories when pharmacologic options for treatment of anxiety or insomnia are considered. Identifying at-risk individuals, considering alternative treatments where appropriate, and education on the safe and effective use of BZDs or Z-drugs may all decrease BZD diversion and misuse (McLarnon 2011). Obtaining patient signature for a treatment contract and monitoring the duration of therapy to limit at 2–6 weeks maximum are another way of preventing BZD-related problems. In addition, a history of respiratory insufficiency such as chronic obstructive lung disease or obstructive sleep apnea should be a relative contraindication to BZDs due to increased lethality in this group.

21.17.3 Patient Education

Education should highlight the side effects of BZDs, including their potential for physical dependence; rebound symptoms upon discontinuation; adverse effect on memory, cognition, and mood; the increased risk of falls; and accidents when operating vehicles or machinery within 24 h of taking the medication.

Prescribers should educate patients and their guardians that a prescription is only for the person who received the prescription, and inform about the risks of diversion including making medications available to other persons living in the household. Education should be provided regarding safe storage of medications in locked cabinets or boxes. Leftover medications should be disposed appropriately and returned to the pharmacist for environmentally safe disposal.

There is a need for widespread education regarding the importance of sleep in children and adolescents and the timely recognition of poor sleep habits and/or sleep problems (Blunden et al. 2004). Sleep hygiene interventions are beneficial in improving sleep quality in children, adolescents, and adults. Combination of sleep hygiene intervention, cognitive behavioral therapy (CBT), and stress reduction has been used to improve sleep and decrease the risk of relapse among adolescents with substance abuse problems (Bootzin and Stevens 2005).

21.17.4 Monitoring of Patients Receiving Prescriptions of BZDs

An office policy should be in place to prevent BZD or Z-drug medications refill beyond 4–6 weeks. Depression should be addressed with specific medications indicated for mood disorders or patients should be referred for mental health treatment.

Pharmacies should be engaged in patient monitoring, especially when filling prescriptions from different practitioners, feeding back this information with the respective practitioners in writing.

Inform patients in writing of the risks of benzodiazepine if prescriptions for benzodiazepine exceed 3 months, obtaining patient signature acknowledging reception of the information or via certified letter.

Programs that offer opiate detoxification may need to screen for concurrent benzodiazepine dependence and modify the detoxification protocol accordingly and address underlying psychiatric issues given their high prevalence in this population.

Clinicians should avoid prescribing sedatives to children, as studies have documented that adolescents who received a medical prescription for sedatives are more likely to use nonprescribed medications of this type. Receiving a prescription reinforces the belief among adolescents that sedatives are "low risk" and that medications are the answers to life's challenges or unpleasant emotions.

21.18 Conclusion

While the true extent of benzodiazepines abuse and diversion is unknown, it is well known that they are among the top most frequently prescribed medications in Western countries and they are used and misused regularly or continuously for insomnia and anxiety and as muscle relaxants. In addition, due to the adverse effects on memory and cognition, BZDs may affect daily activities such as driving or taking care of children. Benzodiazepine abuse leading to dependence is a common and costly comorbidity among substance abuse patients and one for which safe and effective treatments are greatly needed. BZD-related problems are also found among adolescents, seniors, war veterans, and women. Health-care providers and the society in general need to be aware not only of the large abuse liability of these substances but also of the importance of individual differences in risk for misuse and diversion. Detoxification from BDZs is usually a challenging process and needs to be closely monitored by experienced and compassionate providers due to the severe discomfort and the underlying problems that required the medications. Non-pharmacologic therapies such as sleep hygiene, exercise, outdoor activities, cognitive behavioral therapy, mindfulness skills training, or other relaxation interventions have been shown to be as efficacious as pharmacotherapy for insomnia and anxiety. These interventions have the benefits of long-term stress reduction, improvement of cognition and life satisfaction, and decrease in disease burden.

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Treatment of Cannabis Use Disorders

22

Divya Ramesh and Margaret Haney

Contents

Abstract

Cannabis is being used by approximately 5 % of the world's population, and a subset of regular users develop a cannabis use disorder characterized by tolerance, craving, and a withdrawal syndrome. Correspondingly, there is a demand for cannabis treatment that has risen dramatically in recent years. Yet, similar to other drug treatments, the vast majority of patients seeking treatment for their cannabis use fail to achieve abstinence.

The objective of this chapter is to inform clinicians about characteristic features of cannabis use disorders and update them on the current state of treatment research. Psychosocial treatment remains the primary approach utilized, but relatively poor response rates suggest that medications may be a useful

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adjunct to reduce withdrawal symptoms, enhance treatment retention, and reduce relapse. The strategies tested in developing potential treatment medications include agonist substitution, antagonists, or modulators of non-cannabinoid neurotransmitter systems. Preliminary data from human laboratory and clinical studies suggest that the cannabinoid agonist nabilone, the opioid antagonist naltrexone, and the GABAergic drug gabapentin show promise and warrant further clinical investigation. Overall, results from clinical studies highlight the challenges in treating cannabis use disorders and the need to develop more efficacious therapeutic interventions.

22.1 Introduction

Cannabis is being used by approximately 5 % of the world's population, and a subset of regular users develop a cannabis use disorder characterized by tolerance, craving, and a withdrawal syndrome. Correspondingly, there is a demand for cannabis treatment that has risen dramatically in recent years. Yet, similar to other drug treatments, the vast majority of patients seeking treatment for their cannabis use fail to achieve abstinence.

The objective of this chapter is to inform clinicians about characteristic features of cannabis use disorders and update them on the current state of treatment research. Psychosocial treatment remains the primary approach utilized, but relatively poor response rates suggest that medications may be a useful adjunct to reduce withdrawal symptoms, enhance treatment retention, and reduce relapse. The strategies tested in developing potential treatment medications include agonist substitution, antagonists, or modulators of non-cannabinoid neurotransmitter systems. Preliminary data from human laboratory and clinical studies suggest that the cannabinoid agonist nabilone, the opioid antagonist naltrexone, and the GABAergic drug gabapentin show promise and warrant further clinical investigation. Overall, results from clinical studies highlight the challenges in treating cannabis use disorders and the need to develop more efficacious therapeutic interventions.

22.1.1 Cannabis Epidemiology and Pharmacology

Cannabis, obtained from the hemp plant *cannabis sativa*, is the most-used illicit drug worldwide, accounting for 75 % of all illicit drug use. Over the last decade, 2.5–5.0 % of the world's population reported using cannabis, with an estimated 119–224 million users worldwide (UNODC 2012). The highest prevalence of cannabis use is currently in Oceania (Australia and New Zealand) at 9.1–14.6 %, followed by North America (10.8 %), Western and Central Europe (7.0 %), and West and Central Africa (5.2–13.5 %). While the prevalence of cannabis use in Asia (1.0–3.4 %) remains lower than the global average, Asia's large population results in the highest absolute number of users worldwide (approximately 26–92 million).

In terms of production, Afghanistan and Morocco remain the largest global cannabis producers, where direct distribution is targeted to neighboring African, east European, and Asian countries. Most developed nations obtain cannabis from indigenously grown (mostly indoor) crops. In fact, the boom in indoor cannabis production in recent years has resulted in highly potent "exotic" strains of cannabis, popular in North America, Europe, Japan, and Oceania (UNODC 2012). Correspondingly, the average potency of confiscated cannabis in the United States tripled from 1992 to 2008. Laboratory studies show that high-potency cannabis is more reinforcing than low-potency cannabis (Chait and Burke 1994), supporting the idea that increased potency may impact the likelihood of developing problematic patterns of use.

Although epidemiological data suggest that only about 5–9 % of individuals who have tried cannabis develop dependence (compared with 15–25 % for cocaine), the widespread prevalence of cannabis use results in a significant number of dependent individuals (Anthony et al. 1994). Δ^9-tetrahydrocannabinol (THC) is the constituent of cannabis critical to the development of dependence. *Cannabis sativa* contains over 60 cannabinoid compounds, but THC is the primary psychoactive component of the plant and defines cannabis potency. THC binds to cannabinoid type-1 (CB_1) receptors, which are widely expressed throughout the body and densely populated in neural areas related to cognition, learning and memory, motor coordination, attention, and reward (for a review of neurobiology, see Cooper and Haney 2008).

22.1.2 Cannabis Use Disorders in Humans

Cannabis use disorders are defined as a problematic pattern of cannabis use leading to clinically relevant impairment or distress occurring within a 12-month period as manifested by cannabinoid tolerance and withdrawal; increasing amounts of cannabis use over time; inability to control consumption; craving; and recurrent cannabis use having negative implications on social, professional, and educational life (APA 2013).

Symptoms of cannabis withdrawal commonly appear after 24 h of abstinence, reach their peak around 2–6 days, and remit within 2 weeks, although impaired sleep patterns may persist for longer periods (Budney et al. 2004). According to DSM-V, withdrawal is diagnosed if at least three of the following symptoms develop within a week of abstinence: irritability, anger, or aggression; nervousness or anxiety; sleep difficulty (insomnia, disturbing dreams); decreased appetite or weight loss; restlessness; depressed mood; and at least one of the following physical discomforts – abdominal pain, shakiness/tremors, fever, chills, or headache. Additionally, the following symptoms may be observed a week post abstinence: fatigue, yawning, difficulty in concentration, and rebound periods of increased appetite and hypersomnia following initial bouts of appetite loss and insomnia (APA 2013). Cannabis withdrawal symptoms may cause significant distress and most likely contribute to relapse among those seeking treatment for their cannabis use (Haney et al. 2013a).

22.2 Treatment for Cannabis Use Disorders

In recent years, the proportion of people seeking treating for their cannabis use has been steadily increasing. Treatment admissions for cannabis have doubled in the USA in the last decade and tripled in Europe and Australia. Worldwide, it is currently estimated that 25 % of patients presenting for substance use treatment are those with cannabis use disorders (UNODC 2012). The primary approach for treatment is psychosocial, and to date, there is no approved pharmacological treatment to facilitate psychosocial treatment approaches.

22.2.1 Psychosocial Treatment

Research on psychosocial treatments for cannabis use disorders has been ongoing for the last 25 years, and results from these studies have demonstrated that outpatient treatment models can reduce cannabis use and promote abstinence compared to control conditions. In both adults and adolescents, modest success rates have been seen with cognitive behavioral therapy (CBT), motivational enhancement therapy (MET), contingency management (CM), and family-based therapies.

CBT focuses on providing skills necessary to achieve abstinence and cope with stressors and high-risk situations (Marlatt and George 1984; Monti et al. 2002). MET is a non-confrontational approach that aims to build motivation to reduce drug use, by addressing ambivalent feelings towards drug use, which may produce a motivation to change behavior (Miller and Rollnick 2002). Evidence from a series of controlled clinical trials for cannabis use disorders in adults suggests that the combination of CBT and MET achieves greater rates of abstinence than delayed treatment (Budney et al. 2007a). MET-CBT was associated with significantly greater long-term abstinence and reduction in frequency of cannabis use than control treatment, and typically achieved 19–29 % abstinence rates in the 12-month follow-up.

In an effort to improve outcome, several studies have examined the efficacy of CM for treating cannabis use disorders. CM, a process of systematically using positive reinforcement to reinforce abstinent behavior, has been shown to significantly enhance treatment retention and increase periods of abstinence for other drugs of abuse (Petry and Simcic 2002). The results from trials examining the efficacy of CM alone or in combination with MET-CBT for adult cannabis use disorders have shown that inclusion of CM significantly increased rates of abstinence. Specifically, inclusion of CM yielded enhanced abstinence rates to 35–37 % at the 12-month follow-up, whereas MET alone had abstinence rates of 5–10 % (Budney et al. 2007a; Litt et al. 2013).

By contrast, CM was not quite as efficacious for adolescent or young adults mandated to drug treatment. A study by Carroll and colleagues (2012) showed that the combination of CM and CBT was ineffective in improving treatment outcome for cannabis use disorders in young adults involved with the criminal justice system compared to CBT alone. In adolescents (12–18 years) presenting for publically funded treatment programs, a variety of treatment approaches,

alone and in combination (e.g., CBT, MET, CM, family therapy), yielded about 25 % abstinence rates 1 year later regardless of treatment condition (Dennis et al. 2004). These data suggest that maintaining cannabis abstinence may be more difficult in this population relative to adults.

Taken together, psychosocial approaches improve outcomes for people with cannabis use disorders relative to no treatment; however, relapse rates remain high (about 70 %), consistent with abstinence rates for other drugs of abuse. There is clearly a need to increase treatment outcomes by improving the efficacy of currently available treatment options. The development of medications to supplement psychosocial approaches may result in better treatment retention, alleviation of withdrawal symptoms, and a reduction in cannabis use.

22.2.2 Pharmacotherapy

A variety of medications have been investigated for their potential to improve marijuana treatment outcome. Most of the current research is limited to human laboratory models and small open-label or placebo-controlled clinical trials. A variety of human laboratory studies have been conducted to directly assess the effect of medications on different aspects of cannabis abuse (e.g., intoxication, withdrawal, self-administration) in a controlled, medically supervised environment. These studies provide useful information regarding safety and tolerability of medications combined with cannabis as well as provide clinically relevant outcomes to guide the selection of medications to test in expensive and time-consuming clinical trials. In terms of clinical studies, there are a handful of published case reports, open-label treatment studies, and randomized controlled trials assessing the effects of medications for cannabis use disorders. Medications investigated in the these models include cannabinoid substitutes such as dronabinol and nabilone and non-cannabinoid agents, which were selected to treat specific aspects of cannabis withdrawal symptoms or to blunt positive effects of cannabis.

22.2.2.1 Blocking Cannabinoid Intoxication: The Antagonist Approach

One strategy for developing pharmacological treatments for cannabis addiction is to reduce the positive subjective and reinforcing effects of the drug. The CB_1 receptor antagonist, rimonabant, was found to block many behavioral effects of cannabinoids in animals (Compton et al. 1996). In humans, an initial laboratory study found that acute doses of rimonabant dose-dependently blocked the effects of smoked cannabis. Compared to placebo, the highest rimonabant dose tested (90 mg) reduced positive subjective effects and cardiovascular effects of cannabis by around 40 % and 60 %, respectively (Huestis et al. 2001). A follow-up study assessed the effects of daily rimonabant (40 mg) administration over 15 days on responses to smoked cannabis (Huestis et al. 2007). Rimonabant (40 mg) significantly reduced the cardiovascular effects of cannabis on both days 8 and 15 of daily administration relative to placebo. Rimonabant maintenance also reduced cannabis' positive subjective effects on day 8 but not 15. Further, a single dose of

90-mg rimonabant reduced cannabis-induced heart rate increases but did not blunt the positive subjective effects of cannabis, thereby failing to replicate the earlier study. Unfortunately, rimonabant was found to increase the risk of adverse psychiatric reactions (depression, suicidality) in a clinical trial for obesity, so the medication has been removed from the market and further testing is not possible.

An alternative approach to medications directly blocking the cannabinoid receptor is to target neurotransmitter systems that have been implicated in the effects of cannabis. For example, preclinical studies have demonstrated a functional interaction between endogenous opioids and cannabinoids. Opioid antagonists such as naloxone and naltrexone have been shown to attenuate the reinforcing and rewarding effects of cannabinoid agonists in rodents and nonhuman primates. Conversely, in daily cannabis smokers, acute administration of a range of acute naltrexone doses (12–100 mg) enhanced the subjective and cardiovascular effects of cannabis (3.27 % THC) compared to placebo capsules (Cooper and Haney 2010). Yet, repeated naltrexone administration (50 mg), for 2 weeks or longer, appears to blunt positive subjective and reinforcing effects of smoked cannabis (Haney et al. in preparation). Taken together, these results suggest that clinical studies testing maintenance on naltrexone as an adjunct therapy in the management of cannabis use disorders may be warranted.

22.2.2.2 Alleviating Cannabinoid Withdrawal and Preventing Relapse

A variety of potential medications have been investigated for their ability to ameliorate cannabis abstinence symptoms and prevent relapse. Most promising findings are from studies employing a cannabinoid receptor agonist, such as dronabinol or nabilone. The first study using this approach reported that dronabinol (10 mg, five times/day for 6 days) significantly decreased symptoms of cannabinoid withdrawal, such as craving, anxiety, chills, misery, troubled sleep, and decreased food intake, while producing no evidence of abuse liability (Haney et al. 2004); this pattern of effects was subsequently replicated (Budney et al. 2007b). In a follow-up study, dronabinol was administered at a higher dose (20 mg, three times/day for 8 days). The study also incorporated a laboratory measure of relapse, which is operationally defined as cannabis self-administration, at a cost, after a period of abstinence. Dronabinol at this dose decreased symptoms of cannabis withdrawal, such as restlessness, anorexia, and chills, and produced mild intoxication, but did not decrease relapse to cannabis (Haney et al. 2008). In the same study, a combination of oral dronabinol (60 mg/day) and lofexidine (2.4 mg/day), an α_2-adrenergic receptor agonist shown to improve opioid withdrawal symptoms, was evaluated. Lofexidine was tested because preclinical studies showed that clonidine, another adrenergic receptor agonist, reduced cannabinoid withdrawal symptoms in rodents, presumably by reversing enhanced noradrenergic signaling during withdrawal. Lofexidine alone did not robustly attenuate mood symptoms of withdrawal but improved sleep and decreased cannabis relapse. Yet the combination of lofexidine and dronabinol produced the most robust improvements in sleep, withdrawal, craving, and relapse relative to placebo (Haney et al. 2008).

In terms of clinical data, there are two case reports testing long-term cannabis smokers with dronabinol in concert with other medications (Levin and Kleber 2008). One patient was medicated for 6 months with dronabinol (40 mg/day) and divalproex (250 mg/day), a mood stabilizer that reduces irritability and mood swings in bipolar disorder and during alcohol withdrawal. A second patient was maintained on dronabinol (10–15 mg/day) while also receiving venlafaxine (25 mg/day) for depression and modafinil (100 mg PRN) to counter the energy decreases experienced with dronabinol. In both cases, patients achieved and maintained abstinence.

A randomized, placebo-controlled, double-blind, 12-week trial was then conducted (Levin et al. 2011). Participants ($n = 156$) were randomized to either dronabinol (40 mg/day) or placebo following a 1-week placebo lead-in phase; both groups received weekly MET and CBT therapy. All participants reduced cannabis use over time irrespective of treatment, and there was no significant difference between treatment groups in the proportion of participants who achieved 2 weeks of abstinence at the end of the medication phase. However, the dronabinol group had higher treatment retention (77 %) compared to placebo (61 %), and consistent with laboratory studies, withdrawal symptoms were significantly lower in the dronabinol group than placebo.

Given that both the human laboratory and the clinic found that dronabinol decreased withdrawal but did not alter cannabis use, the next study tested nabilone: a cannabinoid agonist with better bioavailability, less individual variability in drug response, and a more predictable dose–response function than dronabinol (Bedi et al. 2012). Nabilone (6, 8 mg/day, for 8 days) significantly reversed withdrawal-induced irritability and disruptions in sleep and food intake (Haney et al. 2013b). Importantly, nabilone maintenance also decreased a laboratory measure of cannabis relapse. These findings are the most promising human laboratory evidence to date, where a single medication improved both cannabis withdrawal symptoms and prevented relapse and suggest that nabilone is a promising candidate for investigation in a clinical trial for cannabis treatment.

In terms of other cannabinoids, a case report presented the effects of cannabidiol, a non-psychoactive cannabinoid constituent of cannabis, on withdrawal symptoms following abrupt cessation of cannabis use in a chronic, heavy cannabis smoker (Crippa et al. 2013). Following maintenance on cannabidiol (300–600 mg/day) for 11 days, the patient demonstrated no self-reported abstinence symptoms. Controlled testing of cannabidiol is needed.

Various non-cannabinoid medications have also been evaluated in controlled inpatient studies for the treatment of cannabis withdrawal, largely with negative results. For example, bupropion, an indirect noradrenergic and dopaminergic agent used for tobacco cessation (150–300 mg/day for 28 days) was found to worsen ratings of irritability, restlessness, depression, and troubled sleep during cannabis withdrawal compared to placebo (Haney et al. 2001).

Since bupropion has stimulant properties that may have exacerbated abstinence-associated agitation and insomnia, subsequent human laboratory studies assessed the effects of medications with sedative properties on cannabis withdrawal and

relapse. Nefazodone and mirtazapine are both antidepressants that enhance noradrenergic and serotonergic activity. During cannabis withdrawal, nefazodone maintenance (450 mg/day for 26 days) decreased certain cannabis withdrawal symptoms (anxiety, muscle pain) but did not alleviate irritability, misery, or troubled sleep (Haney et al. 2003). Mirtazapine (30 mg/day for 14 days), on the other hand, robustly reversed sleep disruption and appetite loss during cannabis withdrawal, but did not improve participants' mood and did not decrease relapse (Haney et al. 2010).

Consistent with the laboratory data, clinical trials with bupropion and nefazodone were also negative. Bupropion (300 mg/day) and nefazodone (600 mg/day) were each compared to placebo in treatment-seeking, cannabis-dependent individuals (Carpenter et al. 2009). Patients ($n = 106$) were randomized to one of the study medications or placebo in this 13-week trial, with 1 week of placebo lead-in, 10 weeks of study medication, and 2 weeks of lead-out. All patients completed weekly sessions with a psychosocial intervention, and around half of the patients completed the 10-week medication phase. Both cannabis use and withdrawal symptoms decreased over time, and there was no effect of bupropion or nefazodone relative to placebo. Results of this clinical trial are, therefore, consistent with the conclusions of laboratory studies.

Venlafaxine and fluoxetine, both antidepressants, have been investigated for their utility in treating cannabis use disorders in those with comorbid depression. A randomized double-blind placebo-controlled trial with depressed cannabis-dependent adolescents ($n = 70$) found no advantage for fluoxetine (10–20 mg/day for 12 weeks) over placebo on either depression or cannabis use outcomes (Cornelius et al. 2010). A subsequent trial in adult patients ($n = 103$) found that extended-release venlafaxine ($\leq$375 mg/day for 12 weeks) was not effective relative to placebo in reducing depression and could potentially increase cannabis use in this population (Levin et al. 2013). Overall, neither laboratory nor clinical studies provide compelling evidence for the utility of antidepressants to treat cannabis use disorders.

Given that anxiety can be a symptom of cannabis withdrawal, the non-benzodiazepine, antianxiety medication, buspirone, was tested in a randomized, controlled clinical trial for cannabis use disorders (McRae-Clark et al. 2009). Cannabis-dependent patients were randomized to buspirone (60 mg/day) or placebo for 12 weeks in conjunction with a psychological intervention (two or three sessions of motivational interviewing during the first 4 weeks). The study reported a high dropout rate (50 %) and no direct effect of buspirone on self-reported anxiety, withdrawal symptoms, or craving. However, exploratory analyses suggested that decreased anxiety over the study predicted cannabis abstinence, indicating that anxiety symptoms may be a useful treatment target.

Divalproex has been investigated in the laboratory and the clinic for its mood-stabilizing properties. Although divalproex (1,500 mg/day for 29 days) decreased cannabis craving during abstinence, the medication worsened ratings of anxiety, irritability, fatigue, and cognitive performance relative to placebo (Haney et al. 2004). Similarly, a double-blind, placebo-controlled pilot study tested

divalproex (250–2,000 mg/day; adjusted to individual response) in combination with CBT for adults ($n = 25$) (Levin et al. 2004). Patients were randomized to either divalproex or placebo for an initial 6-week period after 2 weeks of placebo lead-in. In the 19 patients who completed at least the initial 8 weeks, self-reported irritability, cannabis craving, and cannabis use decreased over time. There was, however, an increased incidence of divalproex-related adverse reactions (fatigue, headaches, drowsiness, and nausea) and poor patient compliance during the trial. These negative results are consistent with the laboratory findings and do not support the clinical utility of divalproex.

Lithium, another mood stabilizer, has also been tested for the treatment of cannabis withdrawal. A small ($n = 9$), open-label, inpatient laboratory study administering lithium (600–900 mg/day for 6 days) reported a reduction in withdrawal signs in 50 % of the participants (Bowen et al. 2005). A second open-label trial maintained cannabis-dependent patients on lithium (1,000 mg/day) in an inpatient setting for 7 days (Winstock et al. 2009). Lithium was generally well tolerated in this short-term inpatient protocol. Although rates of reported withdrawal symptoms were lower and follow-up reports of abstinence higher than in some previous studies, the safety of outpatient lithium administration is a potential concern.

The hormone, oxytocin, is another potential treatment approach, as it has been shown in several preclinical models to reduce drug reinforcement and anxiety-like behavior. A trial is currently under way examining the effects of intranasal oxytocin following preliminary laboratory findings that acute administration of oxytocin (40 IU) alleviated stress-induced reactivity and craving in eight cannabis users (McRae-Clark et al. 2013). This data is supported by findings that oxytocin mediates lithium's effects on cannabis withdrawal.

A case study with the atypical antipsychotic, quetiapine, given to cannabis users with schizophrenia or bipolar disorder reported reduced cannabis use over the course of treatment (Potvin et al. 2004). Quetiapine is a 5-HT_{2A} and D_2 antagonist, a partial agonist at the 5-HT_{1A} receptor, and inhibits the norepinephrine transporter. An inpatient laboratory study evaluating the effects of quetiapine reported that although maintenance (200 mg/day for 15 days) improved sleep quality, increased caloric intake and decreased weight loss during cannabis withdrawal compared with placebo, quetiapine increased cannabis craving and self-administration. These data do not support quetiapine's potential for the treatment for cannabis use disorders (Cooper et al. 2012).

The clinical utility of atomoxetine (a norepinephrine reuptake inhibitor indicated for attention deficit hyperactivity disorder, ADHD) to treat cannabis withdrawal has been investigated in a small open-label study. Atomoxetine (20–80 mg daily for 11 weeks) demonstrated a trend to reduce cannabis use in cannabis-dependent individuals (Tirado et al. 2008). However, the medication produced adverse effects in the majority of patients (nausea, vomiting, dyspepsia, loose stools). A subsequent placebo-controlled trial evaluated the effects of atomoxetine on symptoms of ADHD and cannabis use in cannabis-dependent adults (McRae-Clark et al. 2010). In conjunction with MET, participants received

either atomoxetine ($n = 19$) or placebo ($n = 19$) for 12 weeks. Participants randomized to atomoxetine had greater improvement in ADHD on the Clinical Global Impression-Improvement scale than those treated with placebo, yet there were no significant effects of atomoxetine on self-rated ADHD symptoms or cannabis use outcomes. These results suggest that atomoxetine may improve some ADHD symptoms but does not reduce cannabis use in this population.

A small open-label, 12-week pilot study investigated the effects of the entacapone, an inhibitor of catecholaminergic catabolism, in patients meeting criteria for a cannabis use disorder ($n = 36$). Entacapone (up to 2,000 mg/day, daily and PRN), as acute or maintenance treatment, significantly decreased craving for cannabis in over half of the patients; controlled studies are needed to confirm these findings (Shafa et al. 2009).

A recent open-label treatment study in adolescents tested the antioxidant N-acetylcysteine (NAC), shown in animal studies to reverse alterations to the glutamate system associated with repeated self-administration of a range of addictive drugs. Patients ($n = 24$) received NAC daily (2,400 mg/day) over a 4-week period with no other intervention (Gray et al. 2010). The medication produced some mild-to-moderate side effects but was generally well tolerated. Self-reported cannabis use as well as cannabis craving decreased during treatment with NAC. In a subsequent 8-week double-blind, randomized, placebo-controlled trial, treatment-seeking cannabis-dependent adolescents (ages 15–21 years; $n = 116$) received NAC (1,200 mg) or placebo twice daily as well as CM and brief cessation counseling weekly (Gray et al. 2012). Participants receiving NAC had more than twice the odds of having negative urine cannabinoid results during treatment, compared with those receiving placebo. Exploratory secondary abstinence outcomes (assessing time to first negative urine cannabinoid test and end-of-treatment abstinence) favored NAC but were not statistically significant.

A recent inpatient laboratory study assessing the effects of baclofen, an antispasmodic agent that increases gamma-aminobutyric acid (GABA) signaling, failed to engender any clinical benefits for cannabis withdrawal (Haney et al. 2010). Baclofen (60, 90 mg/day) had few positive effects on mood or behavior, reduced cognitive performance across conditions, and did not reduce cannabis relapse. A case series assessed the effects of baclofen (40 mg/day) in six patients with both cannabis and nicotine dependence (Nanjayya et al. 2010). Common side effects were sedation and lethargy, consistent with the cognitive impairment demonstrated in the laboratory trial. The authors report that the medication was well tolerated and that withdrawal symptoms decreased in patients who maintained abstinence for between 1 and 13 months. However, the negative results of the controlled laboratory study do not support baclofen's potential to treat cannabis use disorders, despite this case findings.

Finally, a recent pilot clinical trial investigated the effects of the GABAergic agonist, gabapentin, for cannabis use disorders (Mason et al. 2012). Patients ($n = 50$) received either gabapentin (up to 1,200 mg/day) or placebo for 12 weeks in addition to manual-guided, abstinence-oriented individual counseling. Relative to placebo, gabapentin significantly reduced cannabis use and decreased

withdrawal symptoms. Gabapentin was also associated with significantly greater improvement in overall performance on tests of executive function.

In summary, a variety of cannabinoid and non-cannabinoid agents have been tested in the laboratory and clinic for their potential to reduce cannabis intoxication, withdrawal, and cannabis use. Most of these medications did not significantly reduce the wide spectrum of cannabis withdrawal symptoms, and some actually worsened them, but several medications showed promise in the human laboratory and in the clinic.

22.3 Conclusion

Prolonged cannabis use can lead to a clinically significant substance use disorder. Over the past 20 years, there has been a steady increase in studies focusing on both psychosocial approaches and medications development for cannabis use disorders. Most psychosocial treatment studies are better than control conditions but nonetheless produce low rates of long-term abstinence. Thus, as with drugs such as nicotine, alcohol, and opioids, adjunct pharmacotherapy is worth exploring to maximize treatment outcome. Among the cannabinoid and non-cannabinoid agents investigated, several appear to have therapeutic potential.

Cannabinoid agonists like dronabinol reduced withdrawal symptoms and improved treatment retention but failed to alter cannabis use in either the laboratory or the clinic. Yet another cannabinoid agonist, nabilone, reduced both laboratory measures of withdrawal and relapse. The advantages of nabilone over dronabinol include higher bioavailability as well as a longer duration of action, both of which are essential features of a potential treatment medication. Thus, its efficacy needs to be further explored in the clinic. Two medications shown to improve alcohol treatment outcome, gabapentin and naltrexone, also show promise. Further clinical studies confirming these promising findings are needed.

In terms of future directions, the inhibition of endocannabinoid catabolic enzymes, fatty acid amide hydrolase (FAAH), and monoacylglycerol lipase reduces cannabinoid withdrawal in animal models of cannabinoid dependence. Unlike cannabinoid substitutes, FAAH inhibitors do not appear to possess abuse liability (for a full review, see Panlilio et al. 2013). There is currently a study under way at Yale University measuring the efficacy of FAAH inhibitors for reducing withdrawal in cannabis-dependent individuals.

The impact of risk factors (both environmental and genetic) that lead to heavy drug use and the factors that make achieving abstinence challenging need to be better understood in order to optimize treatment approaches. Additionally, over 50 % of patients with cannabis use disorders also abuse other drugs such as nicotine and alcohol and have comorbid psychiatric disorders, but most treatment trials select for psychiatrically healthy cannabis users without dependence on other substances. Indeed, a recent laboratory study has shown that cigarette smoking is an important predictor of cannabis relapse in the laboratory and can influence the efficacy of medications used for treating cannabis use disorders (Haney et al. 2013a). In summary, with the growing treatment demand and increasing awareness about the risks of

cannabis abuse, research into treatment of cannabis use disorders is rapidly expanding. Existing evidence suggests that combining psychosocial treatment with a complementary medication is likely to reduce aversive cannabis withdrawal symptoms, prevent relapse, and improve treatment outcome.

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Treatment of Cocaine Addiction

23

David A. Gorelick

Contents

Abstract

Cocaine use disorders represent a substantial clinical and public health burden in many countries, yet there are no well-proven and broadly effective treatments available, and no medication approved for this indication by any national regulatory authority. Psychosocial treatments are the mainstay of care, guided by the general principles of prompt engagement in treatment; minimum duration of 3 months; strict monitoring of cocaine use with consistent consequences for lapses; and engagement of the patient's social network. Contingency management (i.e., reinforcement for abstinence [cocaine-free urine samples] with vouchers or prizes) and cognitive behavior therapy (CBT) have the strongest evidence for efficacy in controlled clinical trials, often doubling the abstinence rate over standard drug counseling. Other interventions with mixed evidence include community reinforcement, motivational enhancement or interviewing, and participation in Cocaine Anonymous. Medications with efficacy in more

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than one controlled clinical trial include disulfiram, oral stimulants in sustained-release formulation, and the anticonvulsant tiagabine. New treatments currently undergoing clinical study include anti-cocaine vaccines and repetitive transcranial magnetic stimulation (rTMS).

23.1 Introduction

Cocaine is a plant alkaloid found in leaves of the coca bush, *Erythroxylon coca*, which grows in the Andes Mountains region of South America. Its psychoactive properties make cocaine one of the most widely used and abused illicit drugs in the world. There were an estimated 17 million cocaine users worldwide in 2011, representing 0.4 % of the 15- to 64-year-old population (United Nations Office on Drugs and Crime 2013). About one-quarter (27 %) were in North America (4.6 million users, 1.5 % prevalence). While use in North America declined by about one-third over the past 5 years, it is increasing in West and Central Europe (4.0 million, 1.2 %); South America (3.3 million users, 1.3 %); Central America and the Caribbean (0.36 million users, 0.7 %); West, Central, and Southern Africa (2.2 million users, 0.7 %); and Oceania (0.37 million users, 1.5 %). Cocaine use remains relatively low in East and Southeast Europe (0.56 million, 0.2 %), North and Eastern Africa (0.03 million, 0.02 %), and Asia (1.3 million, 0.05 %).

Cocaine use is associated with a variety of psychological and physical health problems, resulting in a substantial clinical and public health burden in countries where use is prevalent. About one in six (16 %) cocaine users (via the intravenous or smoked routes of administration) develop addiction (psychological dependence) to the drug, with subsequent psychological (e.g., depression, psychosis) and socio-economic problems (Degenhardt and Hall 2012; Gorelick and Baumann 2014). Physical health problems associated with cocaine use include infectious diseases such as HIV and viral hepatitis (especially with injection use), trauma, cardiovascular disease, and stroke (Degenhardt et al. 2011; Degenhardt and Hall 2012; Gorelick and Baumann 2014). In 2010, cocaine use disorders were associated globally with an estimated 1.09 million years lived with disability (rate of 16 per 100,000 persons) (Vos et al. 2012), 1.1 million disability-adjusted life years (16 per 100,000 persons) (Murray et al. 2012), and 500 deaths (<0.05 per 100,000 persons) (Lozano et al. 2012). Data from longitudinal studies in five different countries (Brazil, Canada, Denmark, France, Italy) suggest that addicted cocaine users have death rates four- to eightfold higher than those of the same age and sex in the general population (Degenhardt et al. 2011), with even higher death rates in the presence of psychiatric comorbidity (Arendt et al. 2011).

Notwithstanding this substantial health burden, there are no widely used, broadly effective treatments for cocaine addiction. No medication is approved for this indication by any national regulatory authority because no medication has met the scientifically rigorous standard of consistent, statistically significant efficacy in adequately powered, replicated, controlled clinical trials. There are little or no

scientific data to guide decisions on many clinically important questions, such as optimal patient-treatment matching, the combination of psychosocial and pharmacological treatment, and the duration of treatment. Little is known about the treatment of special populations, such as pregnant women, the elderly, and those with medical or serious psychiatric comorbidity. The mainstay of treatment is psychosocial, with a variety of approaches being used. This chapter reviews the current state of cocaine addiction treatment.

23.2 Treatment Approaches

23.2.1 Psychosocial Treatment

A variety of psychotherapy approaches and other psychosocial interventions have been evaluated for the treatment of cocaine addiction, almost exclusively in specialized outpatient psychiatric or addiction treatment programs. These include motivational interviewing and motivational enhancement; psychodynamic, interpersonal, and supportive psychotherapy; and cognitive and behavioral therapies such as relapse prevention and contingency management. Some controlled clinical trials show modest, short-term (typically up to 3 months) improvement; longer-term outcomes are rarely evaluated (Dutra et al. 2008; Knapp et al. 2011; Penberthy et al. 2010). A meta-analysis of nine trials (five involving contingency management; three involving comorbid opiate dependence treated with methadone) enrolling 619 outpatients found that active treatment produced a 31.7 % abstinence rate versus 13 % in the comparison groups, for an effect size $d = 0.62$ (95 % CI = 0.16–1.08) (Dutra et al. 2008). A systematic Cochrane review of 27 randomized controlled trials enrolling 3,663 participants found contingency management, especially when combined with cognitive behavior therapy, more effective than other interventions in terms of better treatment retention and reduced cocaine use (Knapp et al. 2011). However, the substantial heterogeneity across studies precluded calculation of effect sizes, specific comparisons between treatments, or evaluation of moderating factors.

Regardless of treatment modality, several nonspecific factors are considered to significantly influence treatment outcome, although there is little direct evidence in support of many factors in the context of cocaine addiction treatment. Perhaps most important, more intensive treatment (e.g., more frequent visits or longer visits [e.g., day hospital]) and longer duration of treatment (minimum of three months) are associated with better outcomes, especially during early abstinence (Simpson et al. 2002; Zhang et al. 2003). However, there may be a ceiling to the long-term benefits of increasing treatment intensity. After 4–6 months, inpatient treatment was no better than day hospital (Schneider et al. 1996), and day hospital no better than 6 h per week of counseling (Coviello et al. 2001).

Other factors associated with better treatment outcome include prompt engagement with the treatment program (ideally, within 24 h of the decision to enter

treatment), nonjudgmental empathy with the patient (Darker et al. 2012), clear and realistic orientation to treatment goals and behavioral expectations, strict monitoring of cocaine (and other psychoactive substance) use (e.g., frequent urine drug testing) with prompt feedback to the patient and consistent consequences for cocaine use, involvement of the patient's social network (to the extent possible), and attention to any concurrent medical, psychiatric, vocational, legal, or social problems (Friedmann et al. 2004). Involvement with peer self-help groups such as Cocaine Anonymous (modeled after Alcoholics Anonymous) is also associated with improved treatment outcome (Weiss et al. 2005).

23.2.1.1 Contingency Management

Contingency management (CM) is a behavioral intervention that provides the patient something of value (i.e., reinforcement) when they perform a specific and measurable desired behavior. CM is used to reinforce either treatment adherence (e.g., clinic attendance, taking of medication, providing a urine sample for drug testing) or treatment outcome (e.g., providing a drug-negative ["clean"] urine sample). The reinforcement is commonly a cash equivalent such as a gift card or voucher exchangeable for an item that will not hinder recovery, e.g., food or small appliance. The cost of implementing CM has been a major barrier to its wide use. To reduce costs, some programs use as reinforcement the chance to win a prize, rather than a prize itself (the so-called "lottery" or "fish bowl" approach). This approach can be as effective as standard reinforcement (Olmstead and Petry 2009).

One of the earliest uses of CM was in the treatment of cocaine addiction (Higgins et al. 2008). A recent systematic review of 19 studies involving 1,664 patients found that CM, when combined with other psychological interventions, significantly improved treatment retention, reduced cocaine use, and had an additive benefit when combined with pharmacological treatment (Schierenberg et al. 2012). Two meta-analyses including 12 studies (820 patients) (Lussier et al. 2006) and seven studies (four included in the other meta-analysis) (370 patients) (Prendergast et al. 2006) found weighted effect sizes for abstinence during treatment of 0.35 (95 % CI 0.27–0.43) and 0.66 (0.44–0.87), respectively, indicating moderate to large effects. CM may be especially useful in promoting medication adherence and bridging the treatment gap until therapeutic medication effects appear (Carroll and Rounsaville 2007). CM is effective in treating cocaine addiction in a broad range of patients, including those with serious psychiatric comorbidity (Petry et al. 2013) or other substance use disorder (Alessi et al. 2011), older patients (Weiss and Petry 2013), and those at a variety of socioeconomic levels (Secades-Villa et al. 2013). CM is also effective when delivered by therapists in the community (Petry et al. 2012) outside a research setting.

23.2.1.2 Cognitive Behavioral Therapy

Cognitive behavioral therapy (CBT) aims to have the patient think differently about their drug use and unlearn ineffective behaviors and to employ cognitive and behavioral techniques to avoid drug use. The focus on high-risk contexts for drug

use, whether emotional states (e.g., depression, anxiety, stress), cognitive states (e.g., low self-efficacy), exposure to drug-associated cues, or acute withdrawal, is sometimes termed relapse prevention or coping skills training (Hendershot et al. 2011). A lapse (initial drug reuse) is not considered a treatment failure, but an opportunity to implement the skills learned to prevent a lapse from becoming a relapse.

CBT is more effective than drug counseling or psychotherapy in most, but not all, comparative studies (Knapp et al. 2011; Penberthy et al. 2010). Focused relapse prevention was no more effective than standard drug counseling in two of three early controlled trials involving a total of 205 patients – the overall meta-analytic effect size was −0.03 (95 % CI −0.17 to 0.11) (Irvin et al. 1999). The addition of CBT to CM does not generally enhance the efficacy of the latter.

23.2.1.3 Community Reinforcement Approach

The community reinforcement approach (CRA) broadens the behavioral approach to treatment beyond drug use to include the patient's total environment and activities, including skills training to enhance drug refusal and problem solving, family relations, social network, employment, and recreation (Knapp et al. 2011). CRA is often combined with CM and CBT as an integrated treatment package, making it impossible in many studies to evaluate the contribution of CRA itself. CRA plus CM is more effective than CRA alone or drug counseling (Knapp et al. 2011; Penberthy et al. 2010).

23.2.1.4 Drug Counseling

Drug counseling is a nonspecific, supportive form of psychotherapy which generally focuses on recovery issues as conceptualized by self-help recovery groups (e.g., Cocaine Anonymous) (Knapp et al. 2008). Some form of drug counseling is often the standard treatment or treatment as usual against which other treatments are compared in clinical trials. In the absence of convincing studies directly comparing the efficacy of individual with group counseling, most community treatment programs and many clinical trials provide group counseling for cost reasons. Drug counseling is not as effective as CM or CBT (Knapp et al. 2011). A large (487 patients), 6-month, multisite clinical trial found weekly individual plus group drug counseling more effective in reducing cocaine use than group counseling alone or combined with cognitive therapy or with supportive-expressive psychodynamically oriented psychotherapy (Crits-Christoph et al. 1999).

23.2.1.5 Motivational Enhancement

Motivational enhancement (ME) and motivational interviewing (MI) are brief (often one or two sessions) interventions that use a supportive, directive approach to enhance motivation for change (Penberthy et al. 2010). These interventions are used in primary care and other nonspecialized settings to initiate engagement in treatment, but the few published clinical trials provide mixed evidence for efficacy, either alone or combined with other psychosocial interventions (Penberthy et al. 2010).

23.2.1.6 Other Psychosocial Treatments

Several other treatment approaches are described in the literature but not well studied, including 12-Step facilitation (Knapp et al. 2011), web-based self-help (Schaub et al. 2011), and Cocaine Anonymous. The latter is a 12-Step, self-help organization modeled on Alcoholics Anonymous (Weiss et al. 2005).

23.2.2 Pharmacological Treatment

The goal of pharmacological treatment is to reduce or eliminate the positive reinforcement (euphoria, "high") from cocaine, reduce or eliminate the desire (craving) to take cocaine, and/or reduce or eliminate the negative reinforcement from cocaine withdrawal. The achievement of these goals does not guarantee treatment success, as the patient must also learn new beneficial ways of living to replace the cocaine-seeking and cocaine-taking behaviors that are being extinguished. Therefore, in clinical practice, medication almost never is used without some psychosocial treatment component. However, there are few data to guide decisions on the type, intensity, and duration of psychosocial treatment accompanying medication. Few controlled clinical trials explicitly compare the efficacy of medication combined with varying (or no) psychosocial treatments (Carroll et al. 2004). A 12-week controlled clinical trial of L-DOPA/carbidopa found better outcome with medication than placebo in patients also receiving contingency management combined with cognitive behavioral therapy (CBT) plus standard clinical management from a nurse, but not in two other groups receiving CBT plus standard clinical care without contingency management or only standard clinical care (Schmitz et al. 2008).

Four pharmacological approaches are potentially useful to achieve these treatment goals (Gorelick et al. 2004): (1) substitution treatment with a cross-tolerant stimulant (analogous to methadone maintenance treatment of opioid dependence), (2) treatment with an antagonist medication that blocks the binding of cocaine at its site of action (true pharmacological antagonism, analogous to naltrexone treatment of opioid dependence), (3) treatment with a medication that functionally antagonizes the effects of cocaine (such as by reducing the reinforcing effects of or craving for cocaine), and (4) alteration of cocaine pharmacokinetics so that less drug reaches or remains at its site(s) of action in the brain.

Most current clinical and research attention focuses on the second and third approaches, i.e., reducing or blocking cocaine's actions, either directly at its neuronal binding site (true pharmacological antagonism) or indirectly by otherwise reducing its reinforcing effects. The first approach has been evaluated in a small number of clinical trials, with mixed results. The fourth approach has shown promise in animal studies and early phase II clinical trials (Gorelick 2012).

Cocaine has two major neuropharmacological actions: blockade of synaptic neurotransmitter transporters (reuptake pumps), thereby inhibiting the uptake of previously released monoamine neurotransmitters and resulting in psychomotor stimulant effects, and blockade of sodium ion channels in nerve membranes, resulting in local anesthetic effects (Gorelick and Baumann 2014).

Cocaine's positively reinforcing effects derive from its blockade of the dopamine reuptake pump, causing presynaptically released dopamine to remain in the synapse and enhancing dopaminergic neurotransmission (Howell and Kimmel 2008). Cocaine's local anesthetic effects are believed to contribute to cocaine-induced kindling, the phenomenon by which previous exposure to cocaine sensitizes the individual so that later exposure to low doses produces an enhanced response.

23.2.2.1 Antidepressants

Tricyclic and other heterocyclic antidepressants are the most studied class of medications for cocaine dependence treatment. Their efficacy is presumed based on both their pharmacological mechanism of increasing biogenic amine neurotransmitter activity in synapses and their amelioration of the depressive symptoms frequently observed among cocaine-dependent individuals seeking treatment (see below for treatment of patients with comorbid depression).

Desipramine is the first and best studied medication for cocaine addiction treatment and is typically dosed at 150–300 mg/day (about 2.5 mg/kg), similar to doses used to treat depression. Meta-analysis suggests no significant efficacy compared with placebo, but with substantial heterogeneity across studies (Pani et al. 2011). Differences in patient characteristics, concomitant treatment, and desipramine plasma concentrations may account for some of the variability in desipramine efficacy. Patients dually dependent on cocaine and opiates may do better on desipramine if their opioid dependence is treated with buprenorphine rather than methadone (Kosten et al. 2005) or if they receive contingency management treatment along with medication (Kosten et al. 2003). There is limited evidence that patients with steady-state desipramine plasma concentrations above 200 ng/mL have poorer outcomes (Khalsa et al. 1993), with better outcomes at concentrations around 125 ng/mL (Kosten et al. 2003).

Experience with other heterocyclic antidepressants provides only limited evidence for efficacy (Pani et al. 2011). Reboxetine and maprotiline, which inhibit norepinephrine reuptake, and mirtazapine, which increases brain serotonin and norepinephrine activity by blocking the autoregulatory α_2-adrenergic and 5-HT_2 receptors, were effective in small open-label trials. Heterocyclic antidepressants not showing efficacy include atomoxetine, which inhibits norepinephrine reuptake; imipramine, the precursor of desipramine; and nefazodone and venlafaxine, which block both serotonin and norepinephrine reuptake.

Heterocyclic antidepressants have not been associated with unexpected or medically serious side effects. While theoretically possible, there is no evidence that patients who relapse to cocaine use while still on medication are at increased risk of cardiovascular side effects (Nelson et al. 1996).

Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, paroxetine, and sertraline, have not been effective in controlled clinical trials, with one exception (Pani et al. 2011; Winstanley et al. 2011). One clinical trial found citalopram (20 mg/day) significantly better than placebo (Moeller et al. 2007). That study, unlike previous studies, used contingency management in addition to cognitive

behavioral therapy, suggesting the important influence of psychosocial treatment on medication efficacy.

Other types of antidepressants have not been found effective in controlled clinical trials (Pani et al. 2011), including monoamine oxidase (MAO) inhibitors such as transdermal selegiline (a selective MAO type B inhibitor which does not require a strict dietary regimen), bupropion (a weak inhibitor of monoamine reuptake that has stimulant-like behavioral effects in animals), and ritanserin, a 5-HT_2 receptor antagonist.

23.2.2.2 Dopamine Agonists (Antiparkinson Agents)

A variety of direct and indirect dopamine agonist medications have been evaluated (Amato et al. 2011), based on the dopamine depletion hypothesis of cocaine dependence (Dackis and Gold 1985), although the data supporting the hypothesis in humans are equivocal (Gorelick 1999). Findings with direct dopamine receptor agonists (primarily at the D_2 subtype) are inconsistent. Bromocriptine, pergolide (a mixed D_1/D_2 agonist), and pramipexole were not effective in one or more controlled clinical trials, while cabergoline and ropinirole were effective in a controlled clinical trial and open-label trial, respectively.

Amantadine is an indirect dopamine agonist that releases dopamine presynaptically and a weak antagonist at the *N*-methyl-D-aspartate glutamate receptor. Only one of more than half-a-dozen controlled clinical trials found amantadine (200–400 mg/day) better than placebo.

The amino acids L-DOPA, a precursor for catecholamine synthesis approved for the treatment of parkinsonism, and L-tyrosine, the precursor of L-DOPA, were not effective in several controlled clinical trials.

23.2.2.3 Disulfiram

Disulfiram increases dopamine concentrations by blocking the conversion of dopamine to norepinephrine by the enzyme dopamine-β-hydroxylase, so it can be considered a functional dopamine agonist (Gaval-Cruz and Weinshenker 2009). Five small controlled clinical trials in cocaine-dependent patients without alcohol dependence (but with concurrent opioid dependence treated with methadone or buprenorphine in four studies) found disulfiram (250 mg/day) significantly better than placebo in promoting cocaine abstinence (Kosten et al. 2013; Pani et al. 2010). However, two recent, larger controlled clinical trials (both in methadone-maintained patients) found no efficacy for disulfiram (Carroll et al. 2012; Oliveto et al. 2011). Some of the heterogeneity in treatment response may be due to genetic factors. One of the recent positive clinical trials found no significant efficacy for disulfiram in the subgroup of patients with the dopamine-β-hydroxylase gene allele that results in low enzyme activity (Kosten et al. 2013). Two other recent small controlled clinical trials in methadone-maintained patients that found no disulfiram efficacy overall did find significant efficacy in subgroups with functional variants in the ankyrin repeat and kinase domain containing 1 (*ANKK1*) and dopamine D_2 receptor (*DRD2*) genes (Spellicy et al. 2013) and α_{1A}-adrenoreceptor (*ADRA1A*) gene (Shorter et al. 2013b).

Although disulfiram is well tolerated in clinical trials, where subjects are carefully screened for medical and psychiatric comorbidity and closely monitored for adverse events, questions have been raised about its safety in routine clinical practice (Malcolm et al. 2008). Several human laboratory studies give conflicting results on the safety of the cocaine-disulfiram interaction (Baker et al. 2007), although recent studies found no clinically significant adverse effects from the triple interactions of cocaine-alcohol-disulfiram (Roache et al. 2011) or cocaine-methadone-disulfiram (Atkinson et al. 2013). These findings suggest that disulfiram may be a promising treatment for cocaine dependence in some subgroups of patients, although raising a caution about potential adverse drug interactions should patients use cocaine while on the medication.

23.2.2.4 Stimulants

Agonist maintenance treatment of cocaine-dependent patients with stimulant medication might be clinically beneficial in reducing cocaine craving and use (Shearer 2008), by analogy with methadone maintenance treatment of opioid dependence or nicotine replacement treatment of tobacco dependence. As with methadone, advantages might include use of the less medically risky oral route of administration (vs. injected or smoked cocaine), use of pure medication of known potency (thus avoiding adulterant effects or inadvertent overdose), and use of a medication with slower onset and longer duration of action (thus avoiding "rush"/"crash" cycling) (Lile 2006).

Several orally active psychomotor stimulants marketed for the treatment of attention deficit hyperactivity disorder (ADHD) or as appetite suppressants have been used to test the substitution approach (Amato et al. 2011; Mariani and Levin 2012). Sustained-release d-amphetamine (30–60 mg daily) was effective in two small controlled clinical trials, while immediate-release d-amphetamine (20–60 mg daily) and methylphenidate (90 mg daily) were not. A controlled clinical trial of the combination of sustained-release d-amphetamine with modafinil found poorer efficacy than with amphetamine alone or placebo (Schmitz et al. 2012). Mazindol, a stimulant approved for appetite suppression with less abuse potential than amphetamines (classified as Schedule IV controlled substance), was ineffective in three controlled clinical trials. None of these studies reported significant adverse effects, suggesting that stimulant substitution treatment might be safe in cocaine-using patients.

Modafinil, used for the treatment of excessive sleepiness in narcolepsy, obstructive sleep apnea, and shift work sleep disorder, is considered a weak stimulant (Schedule IV). Its mechanisms of action are unclear but include some blockade of presynaptic dopamine transporters as well as increases in brain glutamate release and decreases in GABA release (Ballon and Feifel 2006). A small phase II clinical trial found that 400 mg daily significantly reduced cocaine use (Mariani and Levin 2012). A later multisite clinical trial found no significant reduction in cocaine use in the study sample as a whole. However, in the subgroup of subjects without alcohol dependence, both 200 mg and 400 mg daily of modafinil significantly increased the percentage of abstinent days. Modafinil was safe and well tolerated. It does not

appear to evoke cocaine craving or itself produce euphoria. In phase I human laboratory studies, modafinil does not potentiate the effects of cocaine, nor does it alter cocaine pharmacokinetics, except for a decrease in the area under the cocaine plasma concentration-time curve over the first 3 h after intravenous cocaine administration (Donovan et al. 2005). These findings suggest that modafinil could be safely used in selected subgroups of cocaine-using patients.

Cocaine itself could be used for agonist maintenance treatment in a slow-onset formulation or route of administration (Gorelick 1998), in the same way that slow-onset transdermal or transbuccal nicotine is used to treat dependence on rapid-onset smoked nicotine (cigarettes). Oral cocaine salt capsules (100 mg four times a day) significantly attenuated the response to an intravenous cocaine challenge (25 mg) (Walsh et al. 2000). Both cocaine capsules and coca tea are used to treat addiction to coca paste smoking in Lima, Peru (where oral cocaine products are legal) (Llosa 2009). A case series of 50 coca paste smokers in La Paz, Bolivia, reported that chewing 100–200 g of coca leaf per week for a mean of 2 years substantially improved the mental health of one-third of the patients and improved the socioeconomic functioning of almost half (data on cocaine smoking were not reported) (Hurtado-Gumucio 2000).

23.2.2.5 Antipsychotics

The older (the so-called first-generation) antipsychotics, which are potent dopamine receptor antagonists (chiefly D2 [postsynaptic] subtype), do not significantly alter cocaine craving or use, as evidenced by clinical experience with patients with schizophrenia who abuse cocaine while receiving chronic antipsychotic treatment (Brady et al. 1990; Ohuoha et al. 1997). Greater efficacy was expected from the newer "second-generation" antipsychotics, in part because of their broader spectrum of receptor binding (including dopamine D1 and serotonin receptors). However, this promise has not been confirmed in clinical trials of cocaine users without comorbid psychiatric disorders (Amato et al. 2007). A small open-label trial of olanzapine in 21 patients dually dependent on cocaine and opioids (being treated with methadone) reported a decrease in cocaine use in 53.2 % of patients. However, three more recent controlled clinical trials reported no significant advantage for olanzapine over placebo (Amato et al. 2007; Hamilton et al. 2009). Two controlled clinical trials using oral risperidone and one using long-acting injectable risperidone (Loebl et al. 2008) also found no advantage over placebo.

Any antipsychotic should be prescribed with caution to cocaine users because of their potential vulnerability to the neuroleptic malignant syndrome, based on their presumed cocaine-induced dopamine depletion (Akpaffiong and Ruiz 1991). Cocaine users may also be at elevated risk of antipsychotic-induced movement disorders (Duggal 2007; Henderson et al. 2007).

23.2.2.6 Anticonvulsants

Anticonvulsants might be effective in the treatment of cocaine dependence because they increase inhibitory GABA activity and/or decrease excitatory glutamate activity in the brain, both actions that decrease the response to cocaine in the dopaminergic cortico-mesolimbic brain reward circuit (Brown et al. 2013).

Carbamazepine is the most studied anticonvulsant, but the promise of early open-label studies has not been confirmed in controlled trials. Four of five double-blind outpatient trials found no significant effect on cocaine use (Minozzi et al. 2008). Gabapentin was ineffective in three controlled clinical trials, as were lamotrigine and valproic acid in single trials (Minozzi et al. 2008).

Several other anticonvulsants provide more promising results. Tiagabine, which increases GABA activity by blocking its presynaptic reuptake, significantly reduced cocaine use in two controlled clinical trials at doses of 12 or 24 mg daily, but had no effect in a third trial at 20 mg daily (Minozzi et al. 2008). All three trials used concomitant cognitive behavioral therapy. Topiramate, which decreases glutamate activity by blocking AMPA-type glutamate receptors and increases GABA activity (by an unknown mechanism), significantly reduced cocaine use in a controlled clinical trial at up to 200 mg daily, in conjunction with cognitive behavioral therapy (Minozzi et al. 2008). Vigabatrin (γ-vinyl-GABA), which increases GABA activity by inhibiting the breakdown of GABA by GABA transaminase, reduced cocaine use in three small open-label studies and a controlled clinical trial, but not in a larger controlled clinical trial (Somoza et al. 2013). Phenytoin (300 mg daily) significantly reduced cocaine use in one controlled clinical trial, especially at serum concentrations above 6.0 μg/mL (Minozzi et al. 2008).

Baclofen, approved as an antispasmotic, increases GABA activity by acting as an agonist at $GABA_B$ receptors. One controlled clinical trial found that baclofen (60 mg daily) did not significantly reduce cocaine use, except in the subgroup of subjects with heavier cocaine use (Shoptaw et al. 2003).

23.2.2.7 Nutritional Supplements and Herbal Products

The use of amino acid mixtures, either alone or combined with other nutritional supplements (vitamins and minerals), is attractive because of their relative freedom from regulatory oversight, compared to prescription medications, and their perceived safety and absence of side effects. Proprietary mixtures, including tyrosine (the amino acid precursor of L-DOPA) and L-tryptophan (the amino acid precursor of serotonin), have been marketed with claims of efficacy, but a double-blind, 28-day crossover study found no significant effect of tyrosine and tryptophan (1 g of each daily) on cocaine craving or withdrawal symptoms (Chadwick and Gregory 1990). A more recent controlled clinical trial found L-tryptophan, even when coupled with contingency management treatment, no better than placebo in reducing cocaine use (Jones et al. 2004).

23.2.2.8 Other Medications

A wide variety of other medications have been evaluated for the treatment of cocaine dependence, often on the basis of promising case reports or animal studies suggesting that they influenced the reinforcing effects of cocaine.

Ondansetron, a $5\text{-}HT_3$ receptor antagonist approved for the treatment of nausea and vomiting, significantly reduced cocaine use in a small controlled clinical trial, but only at the highest dose (4 mg twice daily) (Johnson et al. 2006). Varenicline,

a partial agonist at α4β2 nicotinic acetylcholine receptors approved for smoking cessation, significantly reduced cocaine use in a small controlled clinical trial (Plebani et al. 2012).

Naltrexone, a μ-opioid receptor antagonist marketed for the treatment of alcohol dependence and opioid dependence, showed some efficacy at 50 mg/day in cocaine-dependent outpatients without alcohol or opioid dependence, but only when combined with relapse prevention therapy (Schmitz et al. 2001).

Doxazosin, an α_1-adrenergic receptor antagonist approved for the treatment of hypertension, when rapidly titrated over 4 weeks to a daily dosage of 8 mg, significantly reduced cocaine use in a recent small, controlled clinical trial (Shorter et al. 2013a).

Numerous medications were no better than placebo in (usually small-scale) controlled clinical trials (Gorelick 2014). These include amlodipine, a calcium channel blocker; mecamylamine, a nicotinic cholinergic receptor antagonist; the acetylcholinesterase inhibitors donepezil and galantamine; propranolol, a beta-adrenergic receptor antagonist; reserpine, a depleter of presynaptic monoamine neurotransmitters; hydergine, an agonist at dopamine and serotonin receptors and antagonist at alpha-adrenergic receptors that stimulates blood flow; pentoxifylline, a phosphodiesterase inhibitor; riluzole, an inhibitor of glutamate release; memantine, an NMDA glutamate receptor antagonist; *N*-acetylcysteine, which increases brain glutamate levels; celecoxib, a nonsteroidal anti-inflammatory drug; lithium; citicholine, which is neuroprotective and increases phospholipid turnover and monoaminergic neurotransmission; and dehydroepiandrosterone (DHEA), an endogenous steroid precursor of androstenedione, itself a precursor of androgenic and estrogenic hormones. DHEA is also a sigma-1 receptor agonist.

23.2.2.9 Medication Combinations

Concurrent use of two different medications might enhance efficacy while minimizing side effects, either by acting on a single neurotransmitter system by two different mechanisms or by acting on two different neurotransmitter systems (Gorelick 2014). Concurrent open-label use of the dopaminergic agents bupropion and bromocriptine in cocaine-dependent outpatients is safe, albeit with little efficacy. Concurrent use of pergolide (a dopamine D_1/D_2 receptor agonist) and haloperidol (a dopamine D_2 receptor antagonist), designed to produce relatively pure D_1 agonist action, also showed efficacy, as did combined use of amantadine and propranolol. The combination of extended-release mixed amphetamine salts and topiramate was significantly better than placebo in achieving three consecutive weeks of abstinence, but there were no individual drug groups to allow evaluation of the origin of the therapeutic effect. The combination of metyrapone, a cortisol synthesis inhibitor, and the benzodiazepine oxazepam tended to reduce cocaine craving and use in a small controlled clinical trial, but the 50 % dropout rate limits the internal validity of the study.

23.2.2.10 Other Physical Treatments

Acupuncture is an ancient Chinese treatment that involves mechanical (with needles), thermal (moxibustion), or electrical (electroacupuncture) stimulation of

specific points on the body surface. The mechanism of action is unknown; speculation has included stimulation of endogenous opioid systems. Acupuncture of the outer ear (auricular) gained popularity as a treatment for drug withdrawal, especially using five standard locations recommended by the National Acupuncture Detoxification Association (NADA): kidney, liver, lung, shen men, and sympathetic. Meta-analyses of nine published studies (six using the NADA locations) did not find a significant benefit of active acupuncture over sham treatment (Gates et al. 2006; Mills et al. 2005).

23.2.3 Special Treatment Situations

23.2.3.1 Mixed Addictions

Concurrent opioid use, including comorbid addiction, is a common clinical problem among cocaine-dependent individuals. Some individuals use cocaine and opioids simultaneously (as in the so-called speedball) to enhance the drugs' subjective effects. Up to 20 % or more of opioid-dependent patients in methadone maintenance treatment also use cocaine for a variety of reasons, including continuation of prior polydrug abuse, replacement for the "high" no longer obtained from opioids, self-medication for the sedative effects of high methadone doses, or attenuation of opioid withdrawal symptoms (Leri et al. 2003). Three different pharmacological approaches have been used for the treatment of dual cocaine and opioid dependence: (1) adjustment of methadone dose, (2) maintenance with another opioid medication, and (3) addition of medication targeting the cocaine dependence.

Higher methadone doses (usually 60 mg or more daily) generally are associated with less opioid use by patients in methadone maintenance. This relationship also holds in general for cocaine use among patients in methadone maintenance (Peles et al. 2006), although exceptions have been reported. Increasing the methadone dose as a contingency in response to cocaine use can be effective in reducing such use (and more so than decreasing the methadone dose in response to a cocaine-positive urine sample).

Buprenorphine is a partial opioid agonist (μ-receptor agonist/κ-receptor antagonist) used for the agonist substitution treatment of opioid dependence (Mattick et al. 2008). Advantages over methadone (a pure μ-receptor agonist) include a milder withdrawal syndrome and higher therapeutic index (i.e., safety in overdose). Some (but not all) studies in patients concurrently dependent on both opioids and cocaine suggest that cocaine use (as well as opioid use) is reduced at higher buprenorphine doses (16–32 mg daily) (Montoya et al. 2004).

Non-opioid medications for the treatment of cocaine dependence frequently are evaluated in methadone- or buprenorphine-maintained, opioid-dependent outpatients because the opioid agonist maintenance component substantially enhances treatment retention and adherence, improving the internal validity of the trial. A variety of the medications discussed earlier, including desipramine, fluoxetine, amantadine, bromocriptine, disulfiram, and bupropion, have been studied in opioid-maintained, cocaine-dependent patients. There is no evidence that such

maintenance treatment significantly influences medication efficacy, but no studies have directly addressed this issue.

Alcohol dependence is a common problem among cocaine-dependent individuals, both in the community and in treatment settings, with rates of comorbidity as high as 90 % (Gorelick 1992a). Alcohol use by cocaine-dependent patients is associated with poorer treatment outcome due to a variety of factors, including production of the toxic psychoactive metabolite cocaethylene (Pennings et al. 2002), stimulation of cocaine craving by alcohol, or alteration of medication metabolism by the hepatic effects of alcohol.

Two medications used in the treatment of alcohol dependence are also effective in the treatment of outpatients concurrently dependent on cocaine and alcohol. Disulfiram substantially decreased both cocaine and alcohol use in two clinical trials and a small case series, but not in a third clinical trial (Gorelick 2014). Naltrexone, a μ-opioid receptor antagonist approved for the treatment of alcohol dependence and opioid dependence, substantially decreased both cocaine and alcohol use at 150 mg daily, but not at 50 mg daily or 100 mg daily, the doses more typically used in treatment of alcohol or opioid dependence. Combined treatment with both disulfiram (250 mg daily) and naltrexone (100 mg daily) significantly improved abstinence from cocaine and alcohol (Pettinati et al. 2008a).

A recent controlled clinical trial found no significant effect of topiramate compared to placebo in reducing cocaine or alcohol use in outpatients with comorbid dependence, although topiramate-treated participants had better treatment retention and were more likely to be cocaine abstinent during the final 3 weeks of the 13-week trial (Kampman et al. 2013).

23.2.3.2 Psychiatric Comorbidity

Treatment-seeking, cocaine-dependent individuals have high rates of psychiatric diagnoses other than another substance use disorder (i.e., psychiatric comorbidity), with rates as high as 65 % for lifetime disorders and 50 % for current disorders. The most common comorbid disorders tend to be major depression, bipolar spectrum, phobias, and posttraumatic stress disorder (Conway et al. 2006). Personality disorders are common among treatment-seeking, cocaine-dependent individuals, with rates as high as 69 %. The most common of these is antisocial personality disorder (Compton et al. 2005).

Antidepressants vary in their efficacy for reducing cocaine use among patients with comorbid major depression, although there are few direct comparisons or controlled clinical trials (Nunes and Levin 2004; Rounsaville 2004). Desipramine, imipramine, and bupropion have usually, but not always, been found effective, whereas SSRIs (e.g., fluoxetine) and mirtazapine are usually not effective. Venlafaxine (150–300 mg daily) and nefazodone (200 mg twice daily) show some efficacy in small clinical trials (Gorelick 2014).

Both anticonvulsant "mood stabilizers" and antipsychotics are used to treat comorbid bipolar disorder and cocaine dependence. Case series and open-label trials suggest that anticonvulsants such as valproate, divalproex, lamotrigine, and carbamazepine have some efficacy in reducing cocaine use in dually diagnosed

patients (Brown et al. 2012) and are more effective than lithium. Combining lithium with an anticonvulsant may be helpful in treatment-resistant patients.

The second-generation antipsychotics show mixed results in cocaine-dependent patients with comorbid bipolar disorder (Nejtek et al. 2008). Quetiapine reduced cocaine use in one of two clinical trials; risperidone reduced cocaine use in one trial. Switching treated patients to aripiprazole did not reduce their cocaine use.

Up to one-fourth of cocaine-dependent adults have either adult ADHD or a history of childhood ADHD (Kollins 2008). Stimulant and dopaminergic medications are the mainstay of treatment for ADHD, suggesting that some of these patients may be self-medicating their ADHD with cocaine. Case series and clinical trials generally find that such medications successfully treat ADHD symptoms and reduce cocaine use in adults: dextroamphetamine (up to 60 mg/day), methamphetamine (15 mg/day), bupropion (up to 100 mg three times a day), and sustained-release methylphenidate (Gorelick 2014).

Although schizophrenia is not a common comorbid psychiatric disorder among cocaine-dependent individuals, cocaine use and abuse are common among treatment-seeking patients with schizophrenia (San et al. 2007). Clinical experience indicates that first-generation antipsychotics, at doses that are effective in the treatment of schizophrenia, do not significantly alter cocaine craving or use.

Several case series and open-label trials suggest that the second-generation antipsychotics, including clozapine, olanzapine, quetiapine, risperidone, and aripiprazole, may be more effective than older (first-generation) antipsychotics in reducing cocaine and other drug use among patients with schizophrenia (San et al. 2007). However, two head-to-head controlled clinical trials found no difference between olanzapine and haloperidol in reducing cocaine use, with each medication reducing cocaine craving in one of the trials. A controlled clinical trial comparing olanzapine and risperidone found a trend favoring greater reduction in cocaine use by olanzapine.

The use of cocaine can exacerbate or provoke antipsychotic-induced movement disorders (Duggal 2007; Henderson et al. 2007) and increase vulnerability to the neuroleptic malignant syndrome (Akpaffiong and Ruiz 1991).

23.2.3.3 Medical Comorbidity

Few data are available to guide the pharmacotherapy of cocaine dependence in medically ill patients, making this an important issue for future clinical research. Prudent clinical practice requires a careful medical evaluation of any patient before starting medication, with special attention to medical conditions common in cocaine-dependent individuals. Such conditions would include viral hepatitis and alcoholic liver disease, which might alter the metabolism of prescribed medications, and HIV infection. The presence of the latter necessitates caution in prescribing medications with a known potential for inhibiting immune function. Clinical experience suggests that buprenorphine (Carrieri et al. 2000) and bupropion can be used safely in HIV-positive patients, although anti-retroviral medications may decrease bupropion plasma concentrations (Hogeland et al. 2007).

23.2.3.4 Gender-Specific Issues

Women tend to be excluded from or underrepresented in many clinical trials of cocaine dependence pharmacotherapy (Gorelick et al. 1998), in part because of concern over risk to the fetus and neonate should a female subject become pregnant. Thus, there is a substantial lack of information about gender-specific issues of pharmacotherapy in general and the pharmacotherapy of cocaine dependence in particular (Helmbrecht and Thiagarajah 2008). Meanwhile, clinicians must deal on an ad hoc basis with the treatment implications of possible gender differences in medication pharmacokinetics (such as those resulting from differences in body mass and composition) and in pharmacodynamics (such as those related to the menstrual cycle or exogenous hormones such as oral contraceptives).

In the absence of directly relevant and systematically collected data, caution should be used when prescribing medications to pregnant women with stimulant dependence and to those with pregnancy potential, keeping in mind both the risks of medication and the risks of continued stimulant use. Some medications proposed for the treatment of cocaine dependence (such as tricyclic antidepressants, bupropion, and buprenorphine) have little potential for morphologic teratogenicity or disruption of pregnancy, although there are few or no data on behavioral teratogenicity. Some medications do pose at least slight risk, such as amantadine (associated with pregnancy complications), lithium (associated with cardiac malformations and neonatal toxicity), anticonvulsants (associated with increased risk of congenital malformations), and antipsychotics (associated with nonspecific congenital anomalies and neonatal withdrawal).

Some medications (e.g., disulfiram, naltrexone) may generate different treatment responses in men versus women (Carroll et al. 2012; Pettinati et al. 2008b). The reasons for such gender differences are poorly understood but may include differences in medication pharmacokinetics, hormonal interactions, or subjects' psychological or socioeconomic status.

23.2.3.5 Age

Although adolescents make up a substantial minority of heavy cocaine users, they have been largely excluded from clinical trials of cocaine pharmacotherapies because of legal and informed consent considerations. On the basis of the scarcity of published case reports, it is likely that medication is not often used in the treatment of adolescent cocaine dependence.

23.2.4 International Perspectives

The prevalence of cocaine use varies substantially by geographic region, based in part on the relative availability of cocaine and of other stimulants (United Nations Office on Drugs and Crime 2013). In addition, national differences in modes of cocaine use result in variation in cocaine addiction and related problems. The acute psychological effects of cocaine, and therefore its abuse liability, depend greatly on the rate at which drug reaches the brain. The more rapid the onset of effect, the more

intense the psychological effect and the greater the abuse liability (Nelson et al. 2006). This is the so-called rate hypothesis of psychoactive drug effect. As expected from this rate effect, routes of administration that produce rapid onset, such as intravenous and smoked, are associated with greater abuse liability than those with slower onset, such as intranasal and oral (Chen and Anthony 2004; Gorelick 1992b). Thus, the Andean countries in which oral cocaine ingestion is legal and common (e.g., by chewing the leaves, drinking coca tea) tend to have less cocaine addiction than might be expected from their prevalence of cocaine use (Montoya and Chilcoat 1996).

The treatment of cocaine addiction is generally comparable worldwide, with the exception of the Andean countries. The legal availability of oral forms of cocaine in those countries makes possible the agonist substitution approach using cocaine itself (Hurtado-Gumucio 2000; Llosa 2009). However, such treatment has never been evaluated in controlled clinical trials.

23.2.5 Future Prospects

Future progress in pharmacological treatment for cocaine dependence is likely to come from the development of new medications with novel or more selective mechanisms of action. New medications should evolve from an improved understanding of the neuropharmacology of cocaine dependence and animal studies of the interactions of cocaine with novel compounds.

Preclinical studies with compounds that bind to the same presynaptic dopamine transporter site as does cocaine (thereby keeping cocaine from acting), but which do not themselves produce robust reinforcing effects (because of slow onset of effect and tight, long-lasting binding), suggest that such compounds may be useful as functional cocaine "antagonists" (Rothman et al. 2008). Manipulation of brain dopamine activity with selective dopamine receptor ligands, especially for the D_3 type, attenuated the rewarding effects of cocaine in several animal studies (Heidbreder and Newman 2010) and awaits the development of compounds suitable for clinical trials. Medications that presynaptically release both dopamine and serotonin also show promise in animal studies (Rothman et al. 2007).

Cocaine administration, like stress, activates the hypothalamic-pituitary-adrenal (HPA) axis, and stress may play a role in relapse to cocaine use after abstinence. These observations stimulated interest in corticotrophin-releasing factor receptor antagonists, some of which reduce cocaine self-administration in animals (Specio et al. 2008).

The endogenous cannabinoid (endocannabinoid) brain neurotransmitter system modulates the dopaminergic reward system (Parolaro and Rubino 2008). The blockade of cannabinoid CB_1 receptors inhibits relapse to cocaine self-administration after abstinence in animals (Wiskerke et al. 2008). Therefore, CB_1 receptor antagonists (or inverse agonists) have promising therapeutic potential if they become available for clinical research, although this will require compounds without the psychiatric side effects seen with previously available agents.

The failure of existing medications to show consistent efficacy in the treatment of cocaine dependence has prompted growing interest in pharmacokinetic approaches, that is, preventing ingested cocaine from entering the brain and/or enhancing its elimination from the body (Gorelick 2012). The former approach could be implemented by active or passive immunization to produce binding antibodies that keep cocaine from crossing the blood-brain barrier. The latter approach could be implemented by administration of an enzyme (e.g., butyrylcholinesterase) that catalyzes cocaine hydrolysis or by immunization with a catalytic antibody. These pharmacokinetic approaches already show promise in attenuating cocaine's behavioral effects in animals. An anti-cocaine vaccine (i.e., active immunization against cocaine) showed promise in significantly reducing cocaine use in a phase II controlled clinical trial (Martell et al. 2009). Further work is needed to increase the consistency of the antibody response and lengthen the duration that antibody concentrations remain high enough to block cocaine use.

Transcranial magnetic stimulation (TMS) involves activation of the brain cells by magnetic fields generated by electromagnetic coils placed on the scalp. Repetitive TMS (rTMS) is approved as a treatment for depression and is under study as a treatment for addiction (Bellamoli et al. 2013). See sidebar for further information.

23.3 Conclusion

The absence of any medication that meets national regulatory standards for efficacy and safety leaves physicians with little clear-cut guidance for pharmacological treatment of stimulant dependence. Among existing medications marketed for other indications, none has yet been proved broadly effective in replicated controlled clinical trials. Disulfiram appears the most promising, especially for patients with comorbid alcohol abuse. Tricyclic antidepressants such as desipramine and imipramine (but not SSRIs such as fluoxetine) may be of use in patients with milder dependence or with comorbid depression. Anticonvulsants such as topiramate, tiagabine, and phenytoin (but not carbamazepine or gabapentin) show promise in controlled clinical trials and warrant further evaluation. The stimulant maintenance approach also warrants further evaluation using medications with low abuse potential (e.g., modafinil or sustained-release methylphenidate or amphetamine) or perhaps even a slow-onset (e.g., oral or transdermal) form of cocaine itself.

More sophisticated patient-treatment matching could enhance the efficacy of current medications by taking into account both patient characteristics that can influence treatment response (e.g., severity of dependence, withdrawal status, psychiatric comorbidity, or concomitant medications) and characteristics of the psychosocial treatment accompanying the medication. For example, a few studies suggest that some medications (e.g., L-DOPA, SSRIs) that are not effective when used with drug abuse counseling or cognitive behavioral therapy may be effective when combined with contingency management treatment (Moeller et al. 2007; Schmitz et al. 2008).

Improved understanding of the neurobiology of dependence should lead to new and more effective medications in the future, possibly by manipulation of the glutamate or endocannabinoid systems or HPA axis or by a pharmacokinetic mechanism. Regardless of which medications show promise in the future, their adoption into clinical practice should be guided by acceptable scientific proof of efficacy and safety, based on data from replicated, well-designed, adequately powered controlled clinical trials. Clinicians should also keep in mind the distinctions between efficacy (treatment works in a research setting in a selected research population getting close attention) and effectiveness (treatment works in a heterogeneous population in a realistic clinical environment) and between a statistically significant and clinically meaningful treatment effect (Miller and Manuel 2008).

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Addiction to Amphetamines and Methamphetamines

24

Ahmed Elkashef

Contents

Abstract

ATS addiction ranks second globally and contributes greatly to the total burden of the disease of addiction. ATS addiction is associated with multiple health problems like HIV and psychiatric diseases like psychosis. Early intervention and treatment provided in an integrated setting promise better outcomes. Data from controlled clinical trials show efficacy for cognitive behavioral therapy (Matrix), motivational enhancement, and contingency management. Agonist medications like d-amphetamine and methylphenidate may have a role in treating ATS withdrawal symptoms and craving, particularly in patients with comorbid ADHD/ADD. Other medications that may be helpful are bupropion and modafinil for low to moderate users. Naltrexone and topiramate are also promising especially for ATS addicts that are also addicted to other substances like nicotine, alcohol, or opiates. Combination of psychotherapy particularly contingency management and pharmacological treatment may offer synergistic effects and have better outcome. The future is promising for better treatments including monoclonal antibodies ad vaccines for the treatment ATS addiction.

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24.1 Introduction

According to the 2012 World Drug Report amphetamine-type stimulants (ATS) use is second only to marijuana as the most widely used illicit substance worldwide. An estimated prevalence of 0.3–1.2 % in 2010, or between 14 million and 52.5 million estimated global users, aged 15–64 years have used ATS at least once in the last year. Regions with the highest prevalence are Oceania and North and Central America. Increases in seizure of methamphetamine are also being reported in East, Southeast, and Central Asia and Transcaucasia (UNODC, World Drug Report 2012).

Methamphetamine and amphetamine have very similar pharmacodynamic effects; either can be metabolized to the other (Anglin et al. 2000; Haile 2007; Rasmussen 2008). Methamphetamine was first synthesized in 1919 by the Japanese pharmacologist Akira Ogata (Cho and Segal 1994). Amphetamine was originally synthesized by the Romanian chemist Lazăr Edeleanu in 1887. Both were used during war to reduce fatigue and were available over the counter in Japan as *Philopon* and *Sedrin*.

Both amphetamine and methamphetamine are highly addictive stimulant that can be easily manufactured in clandestine labs. Following recent clamp down on precursor's purchase, most ATS are now manufactured in super labs and smuggled into different countries. Common street names vary from country to country, e.g., "speed," "meth," "ice," "crystal," "crank," "glass," "Yaba," and "Captagon" just to name few.

ATS are potent dopamine uptake as well as vesicular monoamine transporter (VMAT2) blockers. The latter action is unique to ATS and not shared by other addictive stimulants like cocaine. VMAT2 blockers inhibit the incorporation of synthesized monoamines into the neuronal vesicles which lead to high concentrations of dopamine and other amines in the presynaptic terminal. This leads to higher levels of dopamine release and can also cause oxidative stress and damage to the presynaptic terminals. ATS also inhibit both monoamine oxidases A & B, which in turn makes monoamines more available and prolongs their action.

24.2 ATS-Health-Related Problems

Amphetamine and methamphetamine are approved in the USA and other countries worldwide for the treatment of attention-deficit/hyperactivity disorder, narcolepsy, and obesity. The weak isomer L-methamphetamine is used in the over-the-counter Vick's inhaler.

ATS are powerful stimulants, with short-term effects that include increased alertness, energy, and loss of appetite. Cardiovascular effects include irregular heartbeat, increased heart rate, and blood pressure. Hyperthermia, convulsions, and stroke have also been reported with ATS overdose and can result in death if not treated.

Long-term ATS abuse can lead to addiction and psychosis almost indistinguishable from schizophrenia. Other psychiatric symptoms include chronic anxiety, confusion, insomnia, mood disturbances, and violent behavior. PET studies have shown significant changes in striatal dopamine in chronic methamphetamine users in the form of downregulation or degeneration; these changes were associated with cognitive impairment.

Some of the effects of chronic methamphetamine abuse appear to be, at least partially, reversible. A recent neuroimaging PET study (Volkow et al. 2001) showed recovery in striatal dopamine transporter following prolonged abstinence (2 years, but not 6 months). This was associated with improved performance on motor and verbal memory tests. However, function in other brain regions did not display recovery even after 2 years of abstinence, indicating that some methamphetamine-induced changes are very long-lasting.

Withdrawal symptoms have been reported in patients attempting to stop or entering treatment, include depression, anxiety, fatigue, and an increased craving for the drug.

Injection drug use and risky sexual behavior among methamphetamine users have been associated with increase HIV and hepatitis B and C infections, especially among men who have sex with men. Methamphetamine abuse may also worsen the progression of HIV and its consequences, including greater neuronal injury and cognitive impairment compared with nondrug abusers.

Prenatal exposure to methamphetamine can lead to premature delivery, placental abruption, fetal growth retardation, and heart and brain abnormalities. Ongoing research is continuing to study developmental outcomes such as cognition, social relationships, motor skills, and medical status of children exposed to methamphetamine before birth. However the use of other substances or alcohol and maternal poor nutrition and health make the interpretation of these results difficult.

24.3 Treatment of ATS Addiction

The treatment of ATS addiction as any other addiction should by integrated, comprehensive, individualized, and long term. Psychotherapeutic interventions like contingency management, cognitive behavioral therapy, relapse prevention, Matrix, and 12-step-based therapy that have shown effectiveness in the treatment of other addictions have also shown efficacy in treating ATS addictions. These are detailed elsewhere in this book. Combining medications and psychotherapy like CM have been shown to have synergistic effect and should be incorporated in any treatment plan depending on the treatment setting.

Early intervention will also guarantee better outcomes as most addictions start in adolescence. To guarantee the best care, treatment should also be integrated as possible to address the multiple comorbid mental and physical problems that ATS addicts usually suffer.

In this chapter, we will focus in on psychopharmacological interventions that have been tried so far in the treatment of ATS.

24.3.1 Pharmacological Treatment

24.3.1.1 Agonist Medications

Methylphenidate

A dopaminergic stimulant approved for the treatment of ADHD was tried in methamphetamine dependence. An initial report of efficacy of SR methylphenidate (54 mg) against placebo and aripiprazole for intravenous amphetamine dependence in 20-week randomized trial was not replicated in the larger double-blind study of 79 patients (Tiihonen et al. 2007; Miles et al. 2013). High drop out rates and rigid clinic attendance were cited as possible reasons for the negative outcome. Higher doses of methylphenidate were recommended for future studies.

Dextroamphetamine

Another dopaminergic stimulant approved for weight loss, narcolepsy, and ADHD was tried in two double-blind studies in meth-dependent patients. The first trial used 110 mg of sustained release d-amphetamine daily for 12 weeks with gradual reduction over an additional 4 weeks. Medications were administered daily under supervision. The primary outcome was meth concentration in hair samples at baseline compared to follow-up using hair analysis. Although there was no significant effect for the primary outcomes, there was significantly greater reduction in meth withdrawal symptoms and craving compared to placebo (Longo et al. 2010). Another double-blind study (Galloway et al. 2011) used 60 mg sustained release d-amphetamine for 8 weeks showed no effect for the primary outcome of reducing meth use as evidenced by negative urines. Similar to the first study, this study also reported significant effect on reduction of craving and improving meth withdrawal symptoms for the d-amphetamine group.

Bupropion

The safety of coadministering bupropion and methamphetamine was assessed in a clinical pharmacology study with no evidence of cardiovascular adverse events or PK interaction (Newton et al. 2005). Two double-blind controlled outpatient studies investigated the effects of bupropion SR 150 mg BID in methamphetamine-dependent patients (Elkashef et al. 2008; Shoptow et al. 2008). Significantly, a positive effect in reducing meth use was reported in light users defined as use of 18 days or less/month. The effect was not seen in heavy users defined as >18 days of use in a month or more than two positive urines samples per week on screening. Confirmatory studies are underway.

Modafinil

Modafinil is a weak stimulant approved for the treatment of narcolepsy and obstructive sleep apnea. It is proposed to exert its action on the glutamate and hypocretin system; however, recent PET study suggests that it may also bind to the dopamine transporter. 200 mg of modafinil was tested in a double-blind trial for 10 weeks in 80 methamphetamine-dependent patients. The trial outcomes were negative except for a trend of reducing meth use in those who were medication

compliant and attended counseling sessions (Shearer et al. 2009). In another single blind study, modafinil combined with cognitive behavioral therapy (CBT) for treatment of 13 HIV + gay men with methamphetamine dependence. Six of the ten patients who completed the study reduced their methamphetamine use by over 50 % (McElhiney 2009). Another double blind trial of 400mg Modafinil for 12 weeks, in methamphetamine dependant patients (Henizerling et al. 2010) did not show effect on methamphetamine use.

A more recent multisite trial (Anderson et al. 2011) of 210 meth-dependent patients randomized to placebo, 200 mg or 400 mg of daily modafinil for 12 weeks was conducted. The primary outcome was methamphetamine negative urines per week; patients provided three urine samples weekly. The trial was negative; however, a post hoc analysis showed a significant effect for maximum duration of abstinence (23 days vs. 10 days) favoring modafinil among compliant patients. This study highlights the very important issue of measuring compliance in addiction clinical trials as poor compliance could explain some of the negative outcome.

24.3.1.2 Antagonist Medications

Aripiprazole

A partial agonist second-generation antipsychotic was studied in two human laboratory studies with significant effects on attenuation of subjective effects of orally administered d-amphetamine (Stoops et al. 2006). However, outpatient studies with aripiprazole have been negative. One double-blind randomized study of 15 mg daily had to be stopped prematurely because of high dropout rate and increased amphetamine use (Tiihonen et al. 2007). Another double-blind study of aripiprazole in 90 patients for 12 weeks failed to show significant results (Coffin et al. 2012). These studies don't support a role for aripiprazole in initiating abstinence or use reduction in actively using patients but it may have a role as a relapse prevention medication in abstianing patients.

24.3.2 Other Medications

24.3.2.1 GABA Agonists

Baclofen 60 mg and gabapentin 2,400 mg daily were tried in a double-blind study of 25 meth-dependent patients in a three-arm study for 16 weeks. Neither medication had an effect on reducing methamphetamine use compared to placebo. A post hoc analysis suggests a positive effect in patients who took higher doses of baclofen (Heinzerling et al. 2006). Topiramate a GABA agonist/AMPA antagonist medication was tested in an interaction study with methamphetamine which showed that topiramate enhanced some of the positive effects of methamphetamine. This was attributed to possible PK interaction on methamphetamine metabolism (Johnson et al. 2007). A multisite outpatient trial of topiramate 200 mg for reducing meth use was negative for the primary outcome. However, there was a positive effect in the subgroup of patients that had negative urines at randomization suggesting a role in relapse prevention (Elkashef et al. 2012). Vigabatrin (GVG) was tried in an

open-label study of 30 for 9 weeks. 18/30 subjects completed the study, and 16/18 tested negative for methamphetamine and cocaine during the last 6 weeks of the trial (Brodie et al. 2005). A safety clinical pharmacology interaction study was conducted in non-treatment-seeking methamphetamine-dependent patients given 15 and 30 mg i.v. doses of methamphetamine and doses of GVG up to 5 mg (De La Garza et al. 2009). There were no reports of cardiovascular interactions and no effects of GVG on methamphetamine subjective effects. No published reports currently exist of follow-up outpatient trials of GVG for the treatment of methamphetamine addiction.

Antidepressants

Mirtazapine was tried in a double-blind controlled study in 60 meth-dependent patients for 12 weeks with significant effect in reducing meth-positive urines (Colfax et al. 2011). The SSRIs, fluoxetine, paroxetine, and sertraline were each tried in double-blind controlled studies (Batki et al. 1999, 2000; Piasecki et al. 2002; Rawson et al. 2004; Shoptaw et al. 2006) with no effect on meth use.

Calcium Channels Blockers

Two calcium channel blockers isradipine and amlodipine were tried in human laboratory studies (Johnson et al. 1999; Batki et al. 2002) and reported to reduce the subjective and physiological responses to methamphetamine. However, a controlled outpatient clinical trial of amlodipine failed to show any efficacy in reducing methamphetamine use (Batki 2001).

Ondansetron

A serotonin 5-HT3 receptor antagonist was postulated to reduce dopaminergic release in the striatum. A double-blind multisite, randomized trial of three doses of ondansetron (0.25, 1, or 4 mg twice daily) for 8 weeks combined with CBT failed to show an effect over placebo at decreasing methamphetamine use (Johnson et al. 2008).

Naltrexone

In a human lab study of abstinent meth-dependent patients, naltrexone 50 mg significantly reduced the subjective effects of d-amphetamine (Jayaram-Lindstrom et al. 2007).

In a double-blind placebo-controlled outpatient study of 80 patients with amphetamine dependence, naltrexone 50 mg + relapse prevention therapy was effective in reducing amphetamine use (Jayaram-Lindstrom et al. 2008). Naltrexone plus N-acetyl cysteine were tried in adouble blind placebo controlled trail of 31 patients with methamphetamine dependence for 8 weeks. The primary outcome was reduction in craving (Grant et al. 2010). No effect was reported.

Rivastigmine

Acetylcholinesterase inhibitors have been shown in animal studies to reduce methamphetamine-seeking behavior. Rivastigmine was tried in a 2-week double-blind,

placebo-controlled human laboratory study to study its interactions with methamphetamine 30 mg given i.v. Rivastigmine reduced the cardiovascular and subjective effects of methamphetamine. The 3 mg dosage significantly reduced methamphetamine-induced increases in diastolic blood pressure and self-reports of craving and anxiety. In another controlled study, the same dosage reduced the positive subjective effects of intravenous meth self-administered in human volunteers (De La Garza et al. 2008). Outpatient trials are underway to test its efficacy in reducing meth use.

24.3.2.2 Future Medications Options

VMAT2 inhibitors are being developed as methamphetamine antagonists to block its action on the VMAT receptors. Lobeline a nicotinic alkaloid has been shown in animal studies to decrease self-administration of methamphetamine and block meth-induced dopamine release (Dwoskin et al. 2002; Neugebauer et al. 2007). Tetrabenazine, another VMAT2 inhibitor recently approved in the USA for the treatment of Huntington's disease and other hyperkinetic disorders, is being studied in animal models of addiction. Research is also ongoing for more selective VMAT2 compounds.

CRF-1 antagonists have been shown in preclinical data to block stress-induced relapse through control of cortisol release to alcohol, cocaine, and heroin. The search for a safe CRF-1 antagonist to advance to clinical trials is underway.

D3 antagonists have been shown to block priming, cues, and stress-induced self-administration of nicotine, cocaine, and heroin in animal studies, suggesting a role in relapse prevention in humans. Currently there are no selective D3 antagonists for human trials. Buspirone has been reported in PET studies to have D3 antagonist effect in primates, which may warrant some studies in humans untill a more selective D3 becomes avaialbe.

Cannabinoid-1 (CB-1) receptor antagonists e.g., Rimonabant are another compounds that have been reported to reduce or block self-administration and conditioned cues relapse in preclinical models of THC, nicotine, cocaine, MA, opiates, and ethanol.

Other compounds of interest are group I and group II metabotropic glutamate receptors. mGluR5 antagonists and AMPA receptor antagonists have been shown to block cue-induced relapse to cocaine and heroin in animal models.

Further development of these compounds in man will have far-reaching application in treating substance use disorders particularly polysubstance use.

Cognitive enhancers like D1 agonists, 5-HT 6 antagonists, and D-cycloserine may have a role in strengthening the frontal lobes inhibitory controls on impulsive behavior. They are also expected to improve cognition in ATS-addicted patients.

Other area of therapeutic development for addiction is **immunotherapy**. Vaccines and monoclonal antibodies are in early development for nicotine, cocaine, methamphetamine, and heroin, details of which are highlighted in another chapter.

24.4 Summary

- ATS addiction ranks second globally and contributes greatly to the total burden of the disease of addiction.
- ATS addiction is associated with multiple health problems like HIV and psychiatric diseases like psychosis.
- ATS addiction treatment like other addiction treatment should be started early and should be comprehensive, integrated, and long term.
- Psychotherapeutic interventions like CM, MI, CBT, Matrix, RP, and 12 steps are equally effective for the treatment of ATS addiction and should be utilized as appropriate.
- Agonist medications like d-amphetamine and methylphenidate may have a role in treating ATS withdrawal symptoms and craving, particularly in patients with comorbid ADHD/ADD.
- Other medications that may be helpful are bupropion and modafinil for low to moderate users.
- Naltrexone and topiramate are also promising especially for ATS addicts that are also addicted to other substances like nicotine, alcohol, or opiates.
- There are many trials that are currently in progress for ATS addiction; it is highly recommended that clinicians search the literature periodically for updates prior to initiating medication treatment for their patients.

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Nicotine and Tobacco

25

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Contents

Abstract

Although rates of tobacco use and dependence have been reduced substantially over the past 40 years, one in five Americans continues to smoke. The prevalence of smoking appears to be substantially higher in persons with

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psychiatric and substance use disorders and has remained unchanged, as these smokers have less success in quitting smoking. The epidemiology of tobacco use and dependence and the pharmacological effects of nicotine and tobacco are reviewed followed by a discussion of the clinical assessment of tobacco users. We then review behavioral and pharmacological treatments, including the FDA-approved pharmacotherapies: nicotine replacement therapies (NRTs), sustained-release bupropion, and varenicline. Finally, integration of tobacco dependence treatment into mental health settings is discussed with the view that tobacco dependence is a chronic medical disorder and that more effective treatment of this comorbidity in psychiatric disorders may require targeted treatments based on a better understanding of the pathophysiology of individual psychiatric disorders.

25.1 Introduction

Tobacco smoking is the leading preventable cause of morbidity and mortality in the Western world (Giovino 2007; CDC 2013). In the USA, currently approximately 20 % of the population are tobacco users, which translates to roughly 46 million people. Worldwide, approximately 1.1 billion people use tobacco on a regular basis (George and O'Malley 2004). Around 33 % of those who try cigarettes will become addicted, and 70 % of those people will go on to want to quit completely. Since the release of the Surgeon General's report in 1965, smoking prevalence has been steadily declining, but this reduction appears to have slowed in recent years. Cigarette smoking remains the most common (>90 %) method of tobacco use. In addiction to cigarette smoking, pipe tobacco, cigars, smokeless tobacco, and snus are also common forms of tobacco use. Each year, approximately 450,000 people in the USA die as a result of smoking-attributable medical illnesses such as lung cancer, chronic obstructive pulmonary disease (COPD), cardiovascular disease, and stroke. Additionally, roughly eight million people are sick or disabled because of their cigarette use, and smoking has been estimated to cost the USA $96 billion in smoking-related medical expenses, as well as $97 billion in lost productivity annually (CDC 2013). Smoking is now increasing rapidly throughout the developing world, and it is estimated that current cigarette smoking will cause about 450 million deaths worldwide in the next 50 years. Reducing current smoking by 50 % would prevent 20–30 million premature deaths in the first quarter of this century and 150 million in the second quarter. For most smokers, quitting is the single most important thing they can do to improve their health, and the results of epidemiological studies in Norway suggest that even with sustained reductions (>50 %) in smoking consumption, there is little if any reduction in cardiovascular disease, lung cancer, or other smoking-related cancer risks (Tverdal and Bjartveit 2006), further substantiating the merits of quitting versus reducing smoking.

25.2 The Pathobiology, Clinical Manifestations, and Treatment of Nicotine Dependence

25.2.1 Biology of Nicotinic Receptors

Nicotine is the main psychoactive ingredient in tobacco smoke. When tobacco is smoked, the primary site of action of nicotine is the α4β2 nicotinic acetylcholine receptor (nAChR), which is also activated by the endogenous neurotransmitter acetylcholine. nAChRs in the CNS are pentameric ion channel complexes (Dani et al. 2011) comprised of two α and three β subunits. The seven α subunits are designated α2–α9, and the three β subunits are designated β2–β4. Due to this, there is considerable diversity in subunit combinations, which may explain some of the region-specific and functional selectivity of nicotinic effects throughout the CNS. These pentameric receptors are either homomerically or heteromerically arranged (e.g., $(\alpha4)_3(\beta2)_2$ or $(\alpha7)_5$). Activation of nAChRs leads to Na^+/Ca^{2+} ion channel fluxes and neuronal firing and chronic exposure to nicotine results in desensitization of the receptors. nAChRs are situated presynaptically on several different neurotransmitter secreting neuron types due to their wide dispersement throughout the CNS. Of importance for nicotine addiction are the nAChRs situated on mesolimbic dopamine (DA) neurons that project from the ventral tegmental area (VTA) to the nucleus accumbens (NAc). Activation of nAChRs on mesolimbic DA neurons leads to DA release in the NAc, which helps to facilitate the addictive process involved in chronic tobacco use.

At low concentrations of nicotine, α4β2 nAChR stimulation of afferent GABAergic projections onto mesoaccumbal DA neurons predominates, leading to reduced mesolimbic DA neuron firing and DA release. At higher nicotine concentrations, α4β2 nAChRs desensitize and activation of α7 nAChRs on glutamatergic projections predominates, which leads to increased mesolimbic DA neuron firing and DA secretion. Subsequently, nAChRs desensitize within several milliseconds of activation by nicotine. nAChRs then resensitize after overnight abstinence, which presumably explains why most smokers report that the first cigarette in the morning is the most satisfying. Some recent PET neuroimaging studies have shown that smoking two to three puffs from a cigarette produces saturation of nAChRs in the brain reward system (Brody et al. 2006), while other studies show that smoking to satiety (approximately 2.5 cigarettes) produces saturation (Esterlis et al. 2010). Interestingly, the nAChR saturation levels reached after smoking to satiety are similar to the saturation levels seen after smoking just a few puffs. Therefore, while binding to central nAChRs is an important first step in the effects of nicotine, it is not a complete explanation for continued smoking behaviors.

25.2.2 Clinical Effects of Nicotine and Tobacco

The majority of tobacco users (>90 %) smoke cigarettes. Most of these individuals smoke daily and have some degree of physiological dependence (Rigotti 2002).

However, smoking patterns have changed in recent years, and non-daily smokers now constitute 22–33 % of all adult smokers in the USA (CDC 2008, 2011; SAMHSA 2009). While these non-daily smokers seem dependence resistant, they still show the same difficulty with quitting as daily smokers do (Tindle and Shiffman 2011). Smokers typically describe a "rush" and feelings of alertness and relaxation when smoking, and it is well known that nicotine has both stimulating and anxiolytic effects depending on basal level of arousal. Stimulation of the airway is an aspect of smoking that many individuals will report as reinforcing, and additives such as menthol enhance the experience by increasing the taste and reducing the harshness of smoked tobacco. A diagnosis of nicotine dependence is accomplished clinically by following the criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders IV-TR (DSM IV-TR). These criteria include documentation of daily smoking (typically 10–40 cigarettes per day) for several weeks, evidence of tolerance (e.g., lack of aversive effects of nicotine such as nausea), and the presence of symptoms of nicotine withdrawal upon smoking cessation. Withdrawal symptoms, which peak within 24 hours of cessation and usually subside within 48–72 h, include dysphoria, anxiety, irritability, decreased heart rate, insomnia (waking in the middle of the night), increased appetite, difficulty concentrating, restlessness, and craving for cigarettes. Additionally, most dependent smokers state that they smoke their first cigarette of the day within 5 min of awakening. Use of timeline follow-back procedures (Sobell et al. 1988) and smoking diaries have been used successfully to monitor smoking consumption over time. Scales such as the Fagerstrom Test for Nicotine Dependence (FTND) (Heatherton et al. 1991) allow assessment of the level of nicotine dependence with scores of $\geq$4 on a scale of 0–10 consistent with physiological dependence to nicotine. Nicotine craving and withdrawal can be reliably monitored using validated scales such as the Tiffany Questionnaire for Smoking Urges (Tiffany and Drobes 1991) and the Minnesota Nicotine Withdrawal Scale (Hughes and Hatsukami 1986).

Interestingly, the positive effects of cigarette smoking (e.g., taste, satisfaction) appear to be mediated by non-nicotine components of tobacco such as tar (Dallery et al. 2003). Besides positive reinforcement, withdrawal, and craving, there are several secondary effects of nicotine and tobacco use that may contribute both to maintenance of smoking and to smoking relapse including mood modulation (e.g., reduction of negative affect), stress reduction, and weight control. In addition, conditioned cues can elicit the urge to smoke even after prolonged periods of abstinence (Bedi et al. 2011). Specific effects might be most relevant to individuals high on dietary restraint (weight reduction) and psychiatric disorders (mood modulation, cognitive enhancement, stress reduction). These secondary effects may present additional targets for pharmacological intervention in certain subgroups of smokers (e.g., smokers with schizophrenia, depression, or obesity; George and O'Malley 2004).

25.2.3 Psychosocial Treatments

Several non-pharmacological interventions for smoking cessation are available. These non-pharmacological, or behavioral, treatments available to smokers include telephone quit lines, group and individual counseling, and self-help techniques (Ray et al. 2009a). Behavioral treatments for tobacco dependence can facilitate motivation to quit, provide an emphasis on the social and contextual aspects of smoking, and enhance overall success at smoking cessation (Patten and Brockman 2006). Six-month quit rates with behavior therapies are 20–25 %, and behavior therapy typically increases quit rates up to twofold over control groups. Additionally, providing behavioral support in addition to pharmacotherapy can increase the chance of a successful quit attempt by approximately 10–25 % (Stead and Lancaster 2012). The primary goals of behavioral therapies in the treatment of tobacco dependence include the following: (1) providing necessary skills to smokers to aid them to initiate smoking cessation and (2) teaching skills to avoid smoking in high-risk situations (see Table 25.1).

25.2.3.1 Brief Interventions and Self-help Materials

Brief advice has been found to increase the rate of smoking cessation (USPHS Guidelines, Fiore et al. 2008); therefore, it is recommended that doctors use the five As with all patients (*ask* patients if they smoke, *advise* patients to quit, *assess* patients' motivation level for quitting, *assist* with quit attempts, and *arrange* follow-up contacts). Providing self-help material is a form of brief intervention used to increase motivation to quit and impart smoking cessation skills. Several recent studies have documented that minimal behavioral interventions such as community support groups, telephone counseling, and computer-generated tailored self-help materials can augment smoking cessation rates in controlled settings (Stead and Lancaster 2012). Additionally, the greatest effect may be seen when adding some support (at least four therapy sessions) compared to no support at all (Stead and Lancaster 2012).

25.2.3.2 Motivational Interventions

The goal of motivational interviewing (MI) interventions is to elicit change through addressing ambivalence, increasing intrinsic motivation for change, and creating an atmosphere of acceptance in which patients take responsibility for making changes happen. Brief MI interventions have been developed for smoking cessation (Rollnick et al. 1997), and there is some evidence for increased smoking cessation using MI techniques (Carpenter et al. 2004). MI interventions can also be especially effective for adolescents (Heckman et al. 2010), possibly making MI useful for preventative efforts. Rollnick and colleagues (Rollnick et al. 1997) reported that clinicians found MI interventions to be feasible and acceptable due to the brief nature of the intervention and the focus on patient responsibility and enhancement of the clinician-patient relationship.

Table 25.1 Pharmacological and behavioral treatments for tobacco dependence

Treatment (*FDA-approved)	Mechanism of action	Rating
Nicotine replacement therapies*		
Gum (OTC)	Slow nicotine absorption gradually reduces nicotine craving and withdrawal	1
Transdermal nicotine patch (OTC)	Slow nicotine absorption gradually reduces nicotine craving and withdrawal	1
Lozenge (OTC)	Slow nicotine absorption gradually reduces nicotine craving and withdrawal	1
Vapor inhaler (prescription)	Fast nicotine absorption leads to stimulation of nAChR which rapidly reduces nicotine craving and withdrawal	1
Nasal spray (prescription)	Fast nicotine absorption leads to stimulation of nAChR which reduces craving and withdrawal	1
Non-nicotine pharmacotherapies		
Bupropion SR*	Blocks reuptake of DA and NA; high-affinity, noncompetitive nAChR antagonism reduces nicotine reinforcement, withdrawal, and craving	1
Varenicline*	Acts as a partial agonist of $\alpha_4\beta_2$ nAChRs	1
Nortriptyline	Blocks reuptake of NA and 5-HT; probably reduces withdrawal symptoms and comorbid depressive symptoms; side effects limit utility	1–2
Clonidine	α_2-Adrenoreceptor agonist reduces nicotine withdrawal symptoms	2
Mecamylamine	Noncompetitive, high-affinity nAChR antagonist combined with TNP reduces nicotine reinforcement, craving, and withdrawal	2
Cytisine	Acts as a partial agonist of $\alpha_4\beta_2$ nAChRs, but might have limited efficacy at dose necessary for cessation	2
Naltrexone	Endogenous μ-opioid peptide receptor antagonist reduces nicotine craving and withdrawal in combination with TNP; may reduce alcohol use and obviate cessation-induced weight gain	3
Nicotine vaccine	Limited evidence of efficacy for smoking cessation in early human trials, may also have utility in relapse-prevention	2
Behavioral treatments		
Self-help materials	Increase motivation to quit and impart cessation skills (e.g., community support, telephone counseling)	2
Cognitive behavioral therapy	Behavioral strategies are developed to manage triggers; cognitive coping strategies target maladaptive thoughts to prevent relapse	1
Motivational enhancement therapy	Promotes patient's self-motivational statements, and in turn, patient gains greater awareness of the problems with smoking; increases intention for smoking cessation	2

Effectiveness ratings: 1 = strong evidence to support efficacy; 2 = moderate evidence to support efficacy; 3 = little evidence to support efficacy

25.2.3.3 Cognitive Behavioral Therapies

In CBT (cognitive behavioral therapy), patients learn strategies to anticipate and cope with situations in which they are likely to relapse to smoking. Some degree of efficacy of cognitive behavioral therapies in smokers with and without

psychiatric and substance use disorders has been observed for both individual (Lancaster and Stead 2006) and group (Stead and Lancaster 2005) counseling formats. Additionally, work by Brody and colleagues (2013) has shown that reduced smoking with CBT (without pharmacotherapies) can reduce nAChR densities to normal receptor levels.

25.2.3.4 Relapse Prevention

A large number of smokers relapse within 6 months of quitting, with the majority of smokers relapsing within the first week after a quit attempt (Hughes et al. 2004). Focusing on relapse prevention skills including recognizing high-risk situations and coping with lapses can be included in initial smoking cessation treatment or following a quit attempt. Recent studies have not found an overall benefit for including relapse prevention with smokers after a quit attempt and suggest that more work is needed in this area of treatment research.

25.2.4 Pharmacological Treatments

There are three FDA-approved classes of smoking cessation pharmacotherapies – nicotine replacement therapies (NRTs), sustained-release bupropion, and varenicline. According to the 2008 update to the Public Health Service *Treating Tobacco Use and Dependence Clinical Practice Guideline* (Fiore et al. 2008), five NRTs, as well as bupropion SR and varenicline, all reliably increase cessation rates in comparison to placebo. Several other off-label and novel medications are also discussed in this section (see Table 25.1).

25.2.4.1 Nicotine Replacement Therapies

The goal of nicotine replacement therapy (NRT) is to relieve tobacco withdrawal, by providing nicotine without the harmful effects of cigarette additives, which allows smokers to focus on habit and conditioning factors when attempting cessation. After the acute withdrawal period, nicotine replacement therapy is gradually reduced so that little withdrawal should occur. NRTs rely on systemic venous absorption and so do not produce the rapid high levels of arterial nicotine achieved when cigarette smoke is inhaled. Thus, individuals are unlikely to become addicted to NRTs. NRTs should be discontinued if the person restarts smoking, although safety concerns regarding smoking on patch appear to be less serious than previously thought. All commercially available forms of NRT are effective and increase quit rates by approximately 1.5–2.5-fold compared to placebo (Silagy et al. 2004). The transdermal patch, gum, and lozenge are over-the-counter (OTC), while the nasal spray and inhaler are by prescription. At the time of the writing of this chapter, there are significant changes being proposed for the use of NRTs, including extending their duration of use past 6–12 weeks and removing the recommendation to stop patch use when a smoker relapses to smoking (Sims and Fiore 2002).

Nicotine Gum

Nicotine ingested orally is extensively metabolized on first pass through the liver. Nicotine polacrilex gum avoids this problem via buccal absorption. Because of the ad-lib nature of the nicotine gum, smokers are able to respond immediately to any stressors or cues that may be present in their environment (Piper et al. 2007). Nicotine gum was approved as an OTC medication in the USA in 1996 and contains 2 or 4 mg of nicotine that can be released from a resin by chewing. Nicotine gum should be administered by scheduled dosing (e.g., one piece of 2-mg gum/h). The original recommended duration of treatment was 3 months, though many experts believe longer treatment is more effective. Nicotine absorption from the gum peaks 30 min after beginning to use the gum. Venous nicotine levels from 2- and 4-mg gum are about one third and two third, respectively, of the steady-state (i.e., between cigarettes) levels of nicotine achieved with cigarette smoking. Nicotine via cigarettes is absorbed directly into the arterial circulation; thus, arterial levels from smoking are five to ten times higher than those from the 2- and 4-mg gums. Absorption of nicotine in the buccal mucosa is decreased by an acidic environment, and patients should not use beverages (e.g., coffee, soda, juice) immediately before, during, or after nicotine gum use.

Several placebo-controlled trials established the safety and efficacy of nicotine gum for smoking cessation [reviewed in (Silagy et al. 2004)]. There appears to be some evidence to support using higher doses of nicotine gum (4-mg pieces) in more highly dependent cigarette smokers ($\geq$25 cpd), which supports the idea of matching nicotine gum dose to dependence level of the smoker (Stead et al. 2012).

Side effects from nicotine gum are rare and are mostly limited to those of mechanical origin (e.g., difficulty chewing, sore jaw) or of local pharmacological origin (e.g., burning in the mouth, throat irritation). Tolerance develops to most side effects over the first week, and education about how to properly use the gum (e.g., do not chew too vigorously) decreases side effects.

Nicotine Polacrilex Lozenges

Nicotine lozenges that deliver nicotine (2- and 4-mg preparations) by buccal absorption were approved for OTC use in the USA in 2002. Because of the ad-lib nature of use (similar to that of the nicotine gum), lozenges are able to offer further flexibility for nicotine replacement options for smokers and are known to allow great absorption of nicotine as compared to nicotine gum. Just as with the gum, mild throat and mouth irritation have been reported in preliminary trials (Shiffman et al. 2002). A 6-week double-blind, placebo-controlled RCT of 2- and 4-mg nicotine lozenges has shown their superiority to placebo lozenge (Shiffman et al. 2002), with significant reduction in nicotine craving and withdrawal. Furthermore, high doses of lozenge may be more efficacious in heavily dependent smokers suggesting that lozenge dose can be matched with dependence level.

Nicotine Transdermal Patch

The four transdermal nicotine formulations take advantage of ready absorption of nicotine across the skin. Three of the patches are for 24-h use and one is for 16-h use.

Starting doses are 21–22 mg/24-h patch and 15 mg/16-h patch. Patches are applied daily each morning. Nicotine via patches is slowly absorbed so that on the first day venous nicotine levels peak 6–10 h after administration. Thereafter, nicotine levels remain fairly steady with a decline from peak to trough of 25–40 % with 24-h patches. Nicotine levels obtained with the use of patches are typically half of those obtained by smoking. After 4–6 weeks on high-dose patch (21 or 22 mg/24 h and 15 mg/16 h), smokers are tapered to a middle dose (e.g., 14 mg/24 h or 10 mg/16 h) and then to the lowest dose after 2–4 more weeks (7 mg/24 h or 5 mg/16 h). Most studies suggest that abrupt cessation of the use of patches often causes no significant withdrawal; thus, tapering does not appear to be necessary (Silagy et al. 2004). The recommended total duration of treatment is usually 6–12 weeks.

The overall efficacy of the nicotine transdermal patch (NTP) for smoking cessation has been well documented (Silagy et al. 2004). A meta-analysis of 17 RCTs in 1994 (Fiore et al. 1994) reported end of treatment abstinence rates for NTP of 27 % versus 13 % for placebo patch (OR 2.6) and 22 % versus 9 % at 6-month follow-up (OR 3.0). The effects of active NTP were independent of patch type, treatment duration, tapering procedures, and behavioral therapy format or intensity, though it should be noted that behavioral treatment enhanced outcomes with patch compared to patch alone. Additionally, combining the patch with nicotine lozenge has been shown to produce the greatest benefit for smoking cessation relative to placebo (above that of lozenge alone, patch alone, bupropion SR, and bupropion + nicotine lozenge relative to placebo) (Piper et al. 2009).

Significant adverse events with nicotine patches have not been found, with the most common minor side effects being skin reactions (50 %), insomnia and increased or vivid dreams (15 % with 24-h patches), and nausea (5–10 %). Tolerance to these side effects usually develops within a week of use. Rotation of patch sites helps to decrease skin irritation. Insomnia reported in the first week post-cessation appears to be mostly due to nicotine withdrawal rather than the nicotine patch itself. A 24-h patch can be removed before bedtime to determine if the insomnia is due to the nicotine patch. Without treatment, insomnia usually abates after 4–7 days. There appears to be little dependence liability associated with patch use as only 2 % of patch users continue to use this product for an extended period after a cessation trial (West et al. 2000), and this continued abstinence may be due to the desire to maintain abstinence (Shiffman et al. 2003).

Nicotine Nasal Spray

Nicotine nasal spray is a prescribed NRT that is formulated as a nicotine solution in a nasal spray bottle similar to those used with saline sprays. This NRT was approved for treatment of nicotine dependence in the USA in 1996. Nasal spray delivers droplets that average about 1 mg per administration and is administered (10 mg/ml) to each nostril every 4–6 h. The nicotine spray produces a more rapid rise in nicotine levels than that of nicotine gum but falls below the levels achieved by cigarettes. Peak nicotine levels occur within 10 min, and venous nicotine levels are about two third those of between-cigarette levels. Smokers may use the nasal spray ad lib up to 30 times/day for 12 weeks, including a tapering period.

Randomized, double-blind, placebo-controlled trials of nasal spray versus placebo spray (Silagy et al. 2004) have established the safety and efficacy of the nasal spray for smoking cessation. Both trials employed treatment for 3–6 months, and active nasal spray led to a doubling of quit rates during active use relative to placebo use. Differences were reduced or absent with extended follow-up suggesting the need for maintenance use of this agent. However, maintenance studies with nicotine nasal spray have yet to be published.

The major side effects associated with the use of nicotine nasal spray are nasal and throat irritation, rhinitis, sneezing, coughing, and watering eyes. Nicotine nasal spray may have some dependence liability; in a controlled study by West et al. (2001), prolonged use of nasal spray was determined to be the case in 10 % of smokers using the nasal spray, so follow-up of smokers using nasal spray is recommended.

Nicotine Vapor Inhalers (NVI)

NVI are cartridges (plugs) of nicotine (containing about 1 mg of nicotine each) placed inside hollow cigarette-like plastic rods. When warm air is passed through the cartridges, a nicotine vapor is produced, which is then inhaled. Absorption from nicotine inhaler is primarily buccal rather than respiratory. More recent versions of inhalers produce a rise in venous nicotine levels more rapidly than with nicotine gum but less rapidly than with nicotine nasal spray, with nicotine blood levels of about one third that of between-cigarette levels. Smokers are instructed to puff continuously on the inhaler (0.013 mg/puff) during the day, and recommended dosing is 6–16 cartridges daily. The inhaler is to be used ad lib for about 12 weeks.

No serious medical side effects have been reported with nicotine inhalers. Fifty percent of subjects report throat irritation or coughing. Double-blind, placebo-controlled RCTs (Silagy et al. 2004) have demonstrated the superiority of NVI to placebo inhalers for smoking cessation. Results revealed a two- to threefold increase in quit rates (17–26 %) at trial endpoint compared to placebo inhalers and smaller differences at follow-up periods of 1 year or longer. These data support the short-term efficacy of NVI in cigarette smokers, but longer-term trials with the inhaler are needed, and there is some modest concern about abuse liability, due to long-term use of the product in less than 10 % of smokers (West et al. 2001).

25.2.4.2 Sustained-Release Bupropion

The phenylaminoketone, atypical antidepressant agent bupropion, in the sustained-release (SR) formulation (Zyban®), is a non-nicotine first-line pharmacological treatment for nicotine-dependent smokers who want to quit smoking. The mechanism of action of this antidepressant agent in the treatment of nicotine dependence likely involves dopamine and norepinephrine reuptake blockade (Ascher et al. 1995), as well as antagonism of high-affinity nAChRs (Slemmer et al. 2000). The exact mechanism for bupropion's anti-smoking effects is unclear. The goals of bupropion therapy are as follows: (1) smoking cessation, (2) reduction of nicotine craving and withdrawal symptoms, and (3) prevention of cessation-induced weight gain.

The target dose of this agent in nicotine dependence is 300 mg daily (150 mg bid), and it is typically started 7 days prior to the target quit date (TQD) at 150 mg daily, then increased to 150 mg bid after 3–4 days. Unlike the NRTs, there is no absolute requirement that smokers completely cease smoking by the TQD, though many smokers report a significant reduction in urges to smoke and craving, which facilitates cessation at the time of the TQD when drug levels reach steady-state plasma levels. Some smokers gradually reduce their cigarette smoking over several weeks prior to quitting. Smokers who are faster metabolizers of nicotine (as determined by genetic variation at the CYP2A6 allele) may benefit more from bupropion therapy, as opposed to NRT or counseling (Ray et al. 2009b).

A pivotal multicenter study by Hurt and colleagues (1997) established the efficacy and safety of sustained-release (SR) bupropion for treatment of nicotine dependence which led to its FDA approval in the USA in 1998. In a 7-week double-blind, placebo-controlled multicenter trial, three doses of bupropion SR (100, 150, and 300 mg/day in bid dosing) in combination with weekly individual cessation counseling were given to 615 cigarette smokers using at least 15 cigarettes per day. The end of trial 7-day point prevalence cessation rates for each of the bupropion doses, placebo, 100 mg/day, 150 mg/day, 300 mg/day, were 19.0 %, 28.8 %, 38.6 %, and 44.2 %, respectively. At 1-year follow-up, cessation rates were 12.4 %, 19.6 %, 22.9 %, and 23.1 %, respectively. Bupropion treatment also dose dependently reduced weight gain associated with smoking cessation and significantly reduced nicotine withdrawal symptoms at 150 and 300 mg/day doses.

The primary side effects reported with bupropion administration in cigarette smokers are headache, nausea and vomiting, dry mouth, insomnia, and activation. Many of these side effects are observed in the first week of treatment. The main contraindication for the use of bupropion is a past history of seizures of any etiology. The rates of de novo seizures are low with this agent (<0.5 %) at doses of 300 mg daily or less but have been observed when daily dosing exceeds 450 mg/day.

The combination of bupropion SR with nicotine transdermal patch (NTP) was evaluated in a double-blind, double placebo-controlled, randomized multicenter trial (Jorenby et al. 1999). A total of 893 cigarette smokers, using at least 15 cigarettes per day (cpd), were randomized to one of four experimental groups: (1) placebo bupropion (0 mg/day) + placebo patch; (2) bupropion (300 mg/day) + placebo patch; (3) placebo bupropion + nicotine patch (21 mg/day for 4 weeks, with 2 weeks of 14 mg/day and 2 weeks of 7 mg/day); and (4) bupropion + patch. Bupropion was administered 1 week prior to the target quit date (Day 15) at which time patch treatment was initiated for a total of 8 weeks. All subjects received weekly individual smoking cessation counseling. Cessation rates at the 1-year follow-up assessment were 15.6 % for placebo, 16.4 % for active NTP alone, 30.3 % for bupropion alone, and 35.5 % for the combination of patch and bupropion. Both bupropion + patch and bupropion-alone groups were significantly better than the placebo and patch-alone conditions, but the combination was not significantly better than bupropion alone. Weight suppression after cessation was most robust in the combination therapy group. Side effects were consistent with the profiles of

patch and bupropion, and the combination was well tolerated. However, a higher than expected rate of treatment-emergent hypertension (4–5 %) was noted with the combination of bupropion and patch (Jorenby et al. 1999). Of note, patch-alone treatment was significantly different from placebo at the end of the trial, but not at the follow-up assessments.

Hays et al. (2001) examined the effects of bupropion versus placebo on the prevention of smoking relapse in 784 cigarette smokers who achieved smoking abstinence after a 7-week open-label trial of bupropion (300 mg/day). Abstinent smokers were then randomized to bupropion (300 mg/day) or placebo for a total of 45 weeks. Fifty-nine percent of smokers enrolled in the open-label phase of the trial quit smoking. Significantly more smokers were abstinent at the end of the 52-week treatment period in bupropion versus placebo groups (55.1 vs. 42.3 %, $p < 0.01$), but not at the 1-year follow-up assessment. In addition, days to smoking relapse were higher in the bupropion versus placebo group (156 vs. 65 days, $p < 0.05$). Weight gain was significantly less in the bupropion group at both the end of treatment and 1-year follow-up. The results of this study suggest the efficacy of bupropion in preventing smoking relapse. Data regarding the optimal duration of bupropion therapy for maintenance treatment requires further study.

25.2.4.3 Varenicline

Varenicline tartrate (Chantix® in the USA, Champix® in Europe and Canada), an $\alpha_4\beta_2$ nAChR partial agonist and weak $\alpha 7$ agonist, was approved as a first-line smoking cessation agent by the USFDA in 2006. The results of two independent but identical 12-week Phase III trials comparing varenicline (1 mg bid) to bupropion SR (150 mg bid) and placebo have recently been published (Gonzales et al. 2006; Jorenby et al. 2006). The quit rate for both studies were similar for continuous abstinence over the last 4 weeks (weeks 9–12) of the study: Study 1 (Jorenby et al. 2006) varenicline, 43.9 %; bupropion SR, 29.8 %; and placebo, 17.6 %; Study 2 (Gonzales et al. 2006) varenicline, 44.0 %; bupropion SR, 29.5 %; and placebo, 17.7 %. Quit rates were significantly higher for participants taking varenicline compared to bupropion SR ($ps < 0.0001$), and both drugs resulted in significantly higher quit rates than placebo. Continuous abstinence over the follow-up period (weeks 9–52) was lower, and participants taking varenicline continued to show a higher rate of abstinence (Study 1, 22.1 %; Study 2, 23.0 %) than participants taking bupropion (Study 1, 16.4 %, $p < 0.001$ compared to varenicline; Study 2, 15.0 %, $p = 0.064$ compared to varenicline) and placebo (Study 1, 8.4 %; Study 2, 10.3 %). A third study examining the efficacy of the drug on smoking relapse-prevention used a 12-week open-label varenicline phase followed by randomization to 12 weeks of varenicline or placebo (Tonstad et al. 2006). These investigators found that participants taking varenicline versus placebo were more likely to be continuously abstinent during weeks 13–24 (70.5 % vs. 49.6 %, $p < 0.001$) and weeks 13–52 (43.6 % vs. 36.9 %, $p = 0.02$). Varenicline was found to reduce cravings and smoking satisfaction and to be safe and well tolerated. There were similar discontinuation rates for varenicline and bupropion, and the most common adverse event reported by the varenicline group was nausea (Study 1, 28.1 %; Study 2, 29.4 %).

There have been significant concerns about treatment-emergent neuropsychiatric adverse events such as suicidal and homicidal ideation, psychosis, mania, and aggression with the use of varenicline for smoking cessation. However, reviews of the evidence in clinical treatment (McClure et al. 2010) and evidence from controlled smoking cessation clinical trials in psychiatric populations such as schizophrenia (Williams et al. 2012; Pachas et al. 2012) and bipolar disorder (Wu et al. 2012) suggest the safety of this agent for smoking cessation including in high-risk psychiatric populations. Further research on the safety and utility of these agents in psychiatric and addicted populations is clearly warranted.

25.2.4.4 Off-Label Medications

Cytisine

Cytisine (Tabex® in Europe) is a nicotinic partial agonist that binds with high affinity to the $\alpha_4\beta_2$ nicotinic acetylcholine receptor. West and colleagues (2011) assessed the safety and efficacy of cytisine in the first randomized, placebo-controlled trial for the drug and found that it was significantly more effective for smoking cessation than placebo. Additionally, cytisine is a low-cost treatment and may be an option for those who cannot afford other pharmacotherapy.

Nortriptyline

Nortriptyline is a tricyclic antidepressant which has been shown in several double-blind, placebo-controlled trials to be superior to placebo (Hall et al. 1998; Prochazka et al. 1998) and to have comparable efficacy to bupropion (Hall et al. 2002). Higher intensity behavioral therapies may help to improve its efficacy. The mechanism of action is thought to relate to norepinephrine and serotonin reuptake blockade. Side effects include dry mouth, blurred vision, constipation, and orthostatic hypotension. It appears to have some utility in smokers with past histories of major depression, but its potential for fatal overdose has likely limited its utilization in smokers. However, nortriptyline can be recommended as a second-line agent after nicotine replacement therapies and bupropion, though more study of this agent is necessary.

Clonidine

Clonidine is a presynaptic alpha-2 receptor agonist that dampens sympathetic activity originating at the locus ceruleus. It appears to have efficacy for treating opioid withdrawal and thus was tested with nicotine withdrawal during smoking cessation trials. The most common side effects of clonidine are dry mouth, sedation, and constipation. Postural hypotension, rebound hypertension, and depression are rare with smoking cessation treatment. Several clinical trials tested oral or transdermal clonidine in doses of 0.1–0.4 mg/day for 2–6 weeks with and without behavior therapy and have suggested clonidine is more effective in women than in men. In general, the effects of clonidine have not proven to be as robust as NRTs. An initial study in $n = 71$ heavy smokers by Glassman et al. (1988) showed that at doses up to 0.4 mg/day, cessation rates were doubled in comparison to placebo, and in a follow-up study by this group in $n = 300$ smokers, this initial finding was replicated (Glassman et al. 1993). In fact, a meta-analysis by Covey and Glassman (1991) of

nine placebo-controlled studies and 813 patients found short-term quit rates of 39 % on clonidine versus 21 % on placebo (OR 2.4, 1.7–32.8) and suggested that clonidine was effective in the transdermal preparation and more helpful in female smokers. A subsequent meta-analysis by Gourlay and Benowitz (1995) found long-term follow-up quit rates in four subsequent studies of 31 % on clonidine and 17 % on placebo (OR 2.0, 1.3–3.0). It appears to be useful in reducing nicotine withdrawal symptoms acutely and may have a role in smokers who have high levels or anxiety during early cessation (Niaura et al. 1996). This agent should be considered as a second-line therapy for smokers failing initial treatment with NRTs or bupropion.

Mecamylamine

Mecamylamine (MEC) is a noncompetitive blocker at the ion channel site of both high-affinity central nervous system and peripheral nAChRs. When MEC is given to smokers who are not trying to stop smoking, they initially increase their smoking in an attempt to overcome the blockade produced by this drug. MEC does not precipitate withdrawal in humans perhaps because it is a noncompetitive nAChR antagonist. Common side effects included abdominal cramps, constipation, dry mouth, and headaches. Based on the idea that combined blockade and agonist therapy at the nAChR might be beneficial (similar to the nAChR partial agonist profile of varenicline), two randomized trials were conducted comparing MEC in combination with nicotine patch to placebo and nicotine patch. The rationale of these trials was that MEC would reduce the rewarding effects of nicotine, and the patch would reduce nicotine withdrawal symptoms (Rose et al. 1994, 1998). In the first trial (Rose et al. 1994), MEC (up to 10 mg/day, 5 mg bid for 5 weeks) or placebo was given in combination with nicotine patch (21 mg/day) for up to 8 weeks, and cessation rates were significantly higher in the combination group than the patch-alone group (12/24 [50.0 %] vs. 4/24 [16.7 %], $p < 0.05$). Mecamylamine was reported to reduce cigarette craving and negative affect and appetite increases associated with tobacco withdrawal. In a subsequent study of 80 cigarette smokers (Rose et al. 1998), MEC at doses of up to 10 mg/day was given as a pretreatment for 4 weeks prior to nicotine patch initiation at the TQD, and the combination of MEC and patch was continued for 6 weeks. Similar to the first study, the combination of MEC with NTP increased continuous abstinence rates after the TQD compared to NTP alone (19/40 [47.5 %] vs. 11/40 [27.5 %], $p < 0.05$). These data suggest the efficacy of the combination of MEC with NTP, and this combination should be considered a second-line therapy.

Naltrexone

Naltrexone is a long-acting congener of the μ-opioid receptor antagonist naloxone. The rationale for using naltrexone for smoking cessation is that the performance-enhancing and other positive effects of nicotine may be opioid-mediated (Pomerleau 1998; Krishnan-Sarin et al. 1999). Early studies observed that naltrexone monotherapy increases smoking, presumably an attempt to overcome blockade; however, a study of naltrexone in heavy-smoking alcoholics found that cigarette smoking was decreased modestly (Rosenhow et al. 2003). Adverse events include

elevated liver enzymes, nausea, and vomiting. A trial by Covey and colleagues (1999) in 68 cigarette smokers using at least 20 cpd and highly motivated to quit compared naltrexone (up to 75 mg/day) initiated 3 days prior to the TQD to placebo for a total of 4 weeks. Cessation rates in the naltrexone group were nonsignificantly higher than placebo (46.7 % vs. 26.3 %, $p < 0.10$), and at 6-month follow-up there were no group differences. Recently, treatment with naltrexone has been shown to reduce post-cessation weight gain among women, but not men (King et al. 2012).

Additional promising data with naltrexone was observed with the combination of naltrexone and NRT. A preliminary study by Krishnan-Sarin et al. (2003) suggested that the combination of naltrexone and NTP is superior to NTP alone when NTP administration precedes that of naltrexone (presumably to decrease naltrexone-related withdrawal). In a larger trial of the combination of nicotine patch (21 mg/day) with four active doses of naltrexone (0, 25, 50, and 100 mg/day), it was shown that the highest dose of naltrexone with patch significantly improves continuous smoking abstinence rates compared to placebo (O'Malley et al. 2006), but these effects appeared to be confined to the first weeks of treatment. Further studies of naltrexone either alone or in combination with the patch are needed, including in patients with concurrent alcohol misuse.

Nicotine Vaccines

Nicotine vaccines (Hatsukami et al. 2005) are being developed by a number of companies, but these are not currently available for public use. A systematic review of smoking cessation trials conducted by pharmaceutical companies as part of the drug development process showed that nicotine vaccines, while well tolerated, did not enhance long-term cessation rates (Hartmann-Boyce et al. 2012), and recent Phase III trials of one nicotine vaccine preparation (Nabi Biopharmaceuticals) suggested that these agents did not increase rates of smoking cessation in nicotine-dependent smokers. However, the nicotine vaccine may have promise for the prevention of smoking relapse or initiation of smoking and could be developed for these indications in the future. Side effects include soreness at the injection site and hypersensitivity reactions to vaccine components.

25.2.5 Integration of Tobacco Dependence Treatment into Mental Health-Care Settings

As the high rates of tobacco use and dependence and low rates of smoking cessation are becoming increasingly appreciated in psychiatric and addicted populations (Lasser et al. 2000; Grant et al. 2004; Kalman et al. 2005), it is increasingly evident that mental health and addiction clinics have done little to address the tobacco culture that permeates these institutional environments. However, smoking bans are becoming increasingly common in psychiatric hospitals and addiction treatment programs and appear to be successfully implemented in the majority of reported cases (Lawn and Pols 2005), but these developments have shown little uptake and application in community settings (Mackowick et al. 2012).

The utilization of standard tobacco dependence treatments such as behavioral therapies, NRT, bupropion, and varenicline has been increasingly reported in psychiatric and substance-abusing smokers. For example, various formulations of NRT including nicotine patch (Addington et al. 1998; George et al. 2000; Chou et al. 2004) and nasal spray (Williams et al. 2004) as well as sustained-release bupropion (Evins et al. 2001, 2005; George et al. 2002) and varenicline (Williams et al. 2012; Pachas et al. 2012) have been reported to be well tolerated and efficacious in increasing rates of both smoking reduction and cessation in patients with schizophrenia, when combined with cognitive behavioral and motivational enhancement therapies. Both NRTs and bupropion have also been studied in smokers with major depression (Kinnunen et al. 1996; Hayford et al. 1999; Chengappa et al. 2001), posttraumatic stress disorder (Hertzberg et al. 2001; McFall et al. 2005), and alcohol (Hurt et al. 1995; Hughes et al. 2003; Kalman et al. 2004) and opioid (Shoptaw et al. 2002) dependence to be well tolerated and effective; small trials with bupropion SR (Weinberger et al. 2008) and varenicline (Wu et al. 2012) have suggested their safety and effectiveness in smokers with bipolar illness. Moreover, studies which compared integration of behavioral and pharmacological treatments in a mental health setting for smokers with PTSD found enhanced quit rates compared to nonintegrated smoking cessation therapies (McFall et al. 2005, 2006), suggesting that provision of integrated mental health and tobacco treatment produces enhanced cessation outcomes.

Finally, a better understanding of the pathophysiology of mental disorders may lead to improved treatments for this population. There is increasing evidence that available pharmacological and behavioral treatments, modified for those with mental disorders, can be used safely and effectively in these populations (Mackowick et al. 2012). For example, schizophrenia is associated with a broad range of cognitive deficits particularly those related to prefrontal lobe dysfunction, and atypical antipsychotic drugs (e.g., clozapine, olanzapine) which improve certain cognitive deficits associated with schizophrenia may facilitate reduction of smoking (George et al. 1995; McEvoy et al. 1995; Procyshyn et al. 2002) or smoking cessation with standard pharmacotherapies such as nicotine patch (George et al. 2000) or bupropion SR (George et al. 2002). The development of novel medications which target the underlying pathophysiology of psychiatric or substance use disorders may well lead to important advances in the management of tobacco dependence in these special populations of smokers.

25.3 Conclusion

Tobacco dependence remains one of the leading preventable causes of morbidity and mortality in the Western world. Nonetheless, smoking cessation therapies are among the most cost-effective and proven therapies in psychiatry and medicine. Yet, most health-care providers do not identify tobacco use in their patients. In fact, a survey of psychiatric practices found that only 9.1 % of smokers under the care of psychiatrists received treatment for nicotine dependence (Montoya et al. 2005).

Nonetheless, the American Psychiatric Association has recently published an update of its Clinical Practice Guidelines for Nicotine Dependence (Kleber et al. 2006) which should provide standards for the field of psychiatric in the assessment and treatment of tobacco dependence. Furthermore, while medication and behavioral treatments have documented efficacy in treating tobacco dependence, it is important that these therapies be used in combination to achieve the best overall results and ensure adequate skill acquisition and treatment adherence. Future challenges include developing safer and more effective smoking cessation therapies and making these therapies available to all smokers who want to quit.

25.3.1 Key Points

- Tobacco dependence rates have decreased substantially, but many of the remaining smokers appear to have comorbidities that reduce their chance of quitting such as psychiatric and substance use disorders.
- Identification of smokers in clinical settings is of critical importance to the treatment of tobacco dependence.
- There are effective pharmacological and behavioral therapies for tobacco dependence, which work best when used in combination.
- A better understanding of the pathophysiology of mental health and addictive disorders may lead to improved treatment approaches for tobacco dependence in these smoking populations.
- Smokers with psychiatric and substance use comorbidity may be best treated in settings which integrate smoking cessation treatments with mental health and addiction treatment.

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Addiction to Caffeine and Other Xanthines

26

Thierry Favrod-Coune and Barbara Broers

Contents

Abstract

Xanthine (3,7-dihydro-purine-2,6-dione) is a purine base that can naturally be found in human body tissues and fluids as well as in plants and other organisms. Methylated xanthines (methylxanthines) are phosphodiesterase inhibitors and adenosine receptor antagonists. Methylxanthines have thus different effects: reduce inflammation and immunity, reduce sleepiness and increase alertness, but also stimulate the heart rate and contraction and dilate the bronchi. The most

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well-known methylxanthines are caffeine, methylbromine, and theophylline. Coffee and caffeine withdrawal symptoms exist and are often not recognized, especially in treatment settings, where caffeine withdrawal can be confounded with other symptoms. Caffeine intoxication and withdrawal are recognized clinical entities, but caffeine dependence is currently not. Caffeine withdrawal occurs in half of regular coffee drinkers, even at moderate caffeine intake. The most common symptoms are headache, fatigue, and difficulty to concentrate. Health professionals and patients should be better informed about these symptoms and the risk of occurrence of caffeine withdrawal. There is little research of treatments for clinical problems associated with xanthine use or abuse.

26.1 Introduction

For professionals in the addiction field, discussing the issue of caffeine, in a private or professional context, is a pleasure. Finally there is a domain that allows us to have a sort of positive message: "drink your coffee, it's probably good for you, it's probably good for your patients."

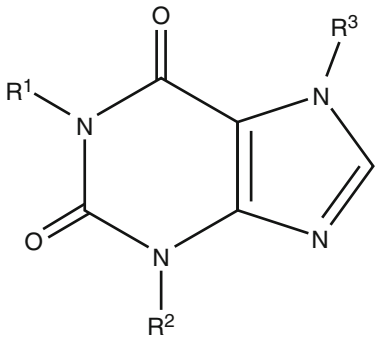
Our image of "controllers" telling in general frightening stories about the risks of smoking, drinking, sniffing, or injecting different psychoactive substances can be slightly improved if we can enchant the benefits of a few cups of espresso in the morning. And it is even better if we can carefully formulate the recommendation not to forget the daily bit of dark chocolate, full of theobromine, another member of the methylxanthine group.

But is this really so? Are we sure there are no acute or long-term risks related to caffeine use? Is there a safe level of use? Should we talk about coffee or caffeine use? Are there subgroups of patients that should avoid xanthine use? And what about caffeine addiction, is it a clinical entity or a popular but misused term?

In this chapter we will focus mostly on caffeine and marginally on other methylxanthines. The objective of this chapter is to describe the effects, risks, and benefits of use of caffeine; discuss "caffeinism and chocoholism"; and provide some clinical recommendations.

26.2 Caffeine and Methylxanthines

Xanthine (3,7-dihydro-purine-2,6-dione) is a purine base that can naturally be found in human body tissues and fluids as well as in plants and other organisms. Methylated xanthines (methylxanthines; *see* Fig. 26.1 *for chemical structure*) are phosphodiesterase inhibitors (increasing intracellular cAMP, activating protein



Caffeine: R1 = R2 = R3 = CH3

Theobromine: R1 = H, R2 = R3 = CH3

Theophylline: R1 = R2 = CH3, R3 = H

Fig. 26.1 Chemical structure of methylxanthines (Source: http://en.wikipedia.org/wiki/File:Methylxanthin_%28R1,_R2,_R3%29.svg)

kinase A, inhibiting the synthesis of tumor necrosis factor (TNF)-alpha and leukotriene) and adenosine receptor antagonists (inhibiting sleepiness-inducing adenosine). Methylxanthines have thus different effects: reduce inflammation and immunity, reduce sleepiness and increase alertness, but also stimulate the heart rate and contraction and dilate the bronchi. The most well-known methylxanthines are caffeine, methylbromine, and theophylline.

Caffeine can be found naturally in coffee beans but also in tea leaves, guarana, and mate plants or kola nuts. Theobromine and theophylline are found in cacao beans and mate plants; tea leaves contain some theophylline. Caffeine and other methylxanthines can be manufactured. Theophylline is a well-known asthma medication, currently used mostly as second line.

Caffeine is absorbed rapidly and completely through the gastrointestinal tract. After oral consumption the plasma peak is after 30–45 min, and the half-time elimination is around 3.5–6 h (Greden 1992) with high variability related to age, hormones, use of nicotine or medications, etc. Metabolization takes essentially place in the liver through the cytochrome P450 pathway, especially through the cytochrome CYP1A2. The deficiency of CYP1A2 enzymes has been shown to impair caffeine metabolism and prolong caffeine half-life (Cornelis et al. 2006), as can certain medications, such as disulfiram (Beach et al. 1986) or quinolones, through CYL1A2 inhibition. Also during pregnancy, the half-life of caffeine increases, with one study suggesting that in the last month of pregnancy, half-life increases to 10.5 h on average (Knutti et al. 1982). Smokers seem to metabolize caffeine more quickly through acceleration of demethylation steps, with normalization of the enzyme-inducing effects of nicotine occurring after 4 days of abstinence (Brown et al. 1988).

Caffeine is metabolized in the liver into 10 % theobromine, 4 % theophylline, and 80 % paraxanthine (Cornish and Christman 1957), so this means that theobromine can be found in the human body even without intake of chocolate.

Only 3 % of caffeine is excreted through the urine.

26.3 Caffeine, Coffee, Tea, and Energy Drinks

Caffeine (1,3,7-trimethylxanthine) taken in coffee and tea can be considered the world's most widely consumed psychostimulant. Over 80 % of the population takes these beverages daily, with important regional differences (Greden and Walters 1992). Coffee is preferred to tea in most developed countries (except in England and Ireland) where 71.5 % of the total amount of coffee of consumed. Tea is (until now) preferred in the developing countries, particularly in Asia, Argentina, Chile, Paraguay, and Uruguay. These countries count for over three quarters of the tea consumption in the world. The total quantity of tea consumed is much higher than coffee, and tea is thus the second beverage consumed after water.

The use of the so-called energy drinks seems to be on the rise especially among young people in the developed world (Reissig et al. 2009; Wolk et al. 2012) and in the sports population, with between 50 % and 70 % of elite athletes taking these drinks (Del Coso et al. 2012). In the USA the sale of energy drinks increased from 100 to 600 million dollars between 2002 and 2006 (Reissig 2009).

It should be kept in mind that coffee and tea contain several other components that can be responsible for potential beneficial and adverse health effects, such as antioxidants (e.g., polyphenols, catechins, flavonoids). Also, the way the beverages are prepared (filtered or unfiltered coffee) and what is added (sugar, milk, creamer, flavors) will have a potential impact on health. Caffeine (mostly artificial) is also added in different soft and energy drinks, as well as in prescribed and over-the-counter medications.

In Europe, the typical dose of caffeine for a cup a coffee is around 60–70 mg; for a cup of tea, 35 mg; for a glass of Coca-Cola, 46 mg; and for an energy drink, about 80 mg (Favrod-Coune and Broers 2010).

In the United States, the average consumption of caffeine is 280 mg per day, which is the equivalent of two cups of filtered coffee per day. Soft drinks contain variable amounts of caffeine, but official FDA limits are 71 mg per drink of 12 oz (355 mL). The so-called energy drinks can contain up to 300 mg of caffeine per drink of 250 mL and up to 500 mg for a bottle (Reissig 2009) (*see* Table 26.1 *for caffeine content of selected foods, beverages, and drugs*).

Individuals taking four or more cups of coffee per day (over 1,000 mg of caffeine daily) are considered to be heavy coffee users (Kabagambe et al. 2013).

With regard to chocolate consumption, inhabitants of Central Europe are considered the champions with over 10 k of chocolate taken per year, whereas in most Asian countries the average citizen takes less than 200 g of chocolate

Table 26.1 Caffeine content in selected food, beverages, and drugs

Product	Serving size	Caffeine per serving (mg)	Caffeine (mg/L)
Percolated coffee	207 mL (7 US fl oz)	80–135	386–652
Drip coffee	207 mL (7 US fl oz)	115–175	555–845
Coffee, decaffeinated	207 mL (7 US fl oz)	5–15	24–72
Coffee, espresso	44–60 mL (1.5–2.0 US fl oz	100	1,691–2,254
Coffee, espresso decaffeinated			
Tea – black, green, and other types – steeped for 3 min	177 mL (6 US fl oz)	22–74	124–416
Guayakí yerba mate (loose leaf)	6 g (200 US fl oz)	Approx. 358	
Hot cocoa	207 mL (7 US fl oz)	3–13	14–62
Hershey's special dark chocolate (45 % cacao content)	1 bar (43 g or 1.5 oz)	31	–
Hershey's milk chocolate (11 % cacao content)	1 bar (43 g or 1.5 oz)	10	–
Coca-Cola classic or diet	355 mL (12 US fl oz)	34	96
Mountain dew	355 mL (12 US fl oz)	54	154
Guaraná Antarctica	355 mL (12 US fl oz	30	100
Red Bull	250 mL (8.5 US fl oz)	80	320
Cocaine energy drink	250 mL (8.5 US fl oz)	288	1,152
Caffeine tablet (regular strength)	1 tablet	100	–
Caffeine tablet (extra strength)	1 tablet	200	–
Excedrin tablet	1 tablet	65	–

References: Kabagambe 2013 and http://en.wikipedia.org/wiki/Caffeine with different validated sources

per year. According to the International Cocoa Organization (www.icco.org), the world per caput consumption of cocoa has increased over the last 10 years, from 0.54 kg in 2002/2003 to 0.61 kg in 2010/2011. For the average Brit, German, or Swiss, cocoa consumption is estimated to be around 5 k per year (13 g daily).

26.4 Main Effects of Caffeine

Caffeine is mostly taken for its psychostimulating properties: it increases alertness, energy, and ability to concentrate, also in those working in night shifts and suffering from jetlags (Ker et al. 2010).

A normal portion of chocolate has also this "arousing" effect, probably through the combined effect of caffeine and theobromine (Smit et al. 2004). The counter side of the stimulating effect of caffeine is the occurrence of sleeping difficulties, with little or no tolerance developing for this effect.

Caffeine increases physical performance, with different studies suggesting that even at 1–2 mg of caffeine per kg of body weight (around one 250 mL serving of an energy drink), reaction time, alertness, and aerobic and anaerobic performance are improved. At higher dose (3 mg caffeine/kg body weight), the ability to repeatedly sprint and the distance covered at high intensity improve, and the jump height increases (Del Coso et al. 2012).

The cardiovascular effects of caffeine include mainly the acceleration of heart rate and increase of force of contraction, with heavy caffeine use potentially triggering tachycardia and arrhythmia in susceptible persons. Anxiety and panic attacks occurring after (in general high dose of) coffee intake can be related to both the psychostimulating effect and tachycardia induced by caffeine (Kabagambe et al. 2013).

With regard to gastrointestinal effects, caffeine will increase gastric secretion and gastric acidity, possibly influencing absorption of different nutritional and pharmacological elements (e.g., iron), but most studies have been inconclusive. Caffeine stimulates the smooth muscles, thus impacting on bowel function and decreasing constipation (Kabagambe et al. 2013).

Caffeine definitely has a diuretic effect, an effect that is rapid and strong. Probably both gastric and urinary discomforts contribute to spontaneous cessation of coffee intake in the elderly (Greden 1992).

26.5 Risks of Caffeine Use

26.5.1 Acute Risks

Caffeine has a low risk profile, but after intake of large quantities (over 250 mg), especially in non-tolerant subjects, an overstimulation of the central nervous and the cardiovascular system can occur, resulting in what is called a "caffeine intoxication." This clinical entity is mentioned in both the Diagnostic and Statistical Manual of Mental Disorders (DSM) and International Classification of Diseases (ICD).

In DSM-IV, the caffeine-related disorders are as follows:

292.89 – induced anxiety disorder
292.89 – induced sleep disorder
305.90 – intoxication
292.9 – related disorder NOS

For the ICD-10 criteria of caffeine intoxication, please see Table 26.2.

The incidence of caffeine intoxication seems to be increasing; it occurs mainly in young patients, mainly due to the use of caffeine-containing medications or energy drinks (not due to coffee intake), and when hospitalization is necessary, there is in general co-occurring use of other psychoactive substances or pharmaceutical products (McCarthy et al. 2008). Death from caffeine overdose has been described (Holmgren et al. 2003), but it is not clear if in these cases patients have taken medications or have genetic cytochrome abnormalities

Table 26.2 ICD 10 criteria for intoxication and withdrawal state of caffeine and other stimulants (other than cocaine, F 14.0)

F15.0 Acute intoxication due to use of other stimulants, including caffeine
A. The general criteria for acute intoxication (F1x.0) must be met
B. There must be dysfunctional behaviour or perceptual abnormalities, as evidenced by at least one of the following
(1) Euphoria and sensation of increased energy
(2) Hypervigilance
(3) Grandiose beliefs or actions
(4) Abusiveness or aggression
(5) Argumentativeness
(6) Lability of mood
(7) Repetitive stereotyped behaviours
(8) Auditory, visual, or tactile illusions
(9) Hallucinations, usually with intact orientation
(10) Paranoid ideation
(11) Interference with personal functioning
C. At least two of the following signs must be present
(1) Tachycardia (sometimes bradycardia)
(2) Cardiac arrhythmias
(3) Hypertension (sometimes hypotension)
(4) Sweating and chills
(5) Nausea and vomiting
(6) Evidence of weight loss
(7) Pupillary dilatation
(8) Psychomotor agitation (sometimes retardation)
(9) Muscular weakness
(10) Chest pain
(11) Convulsions
F15.3 Withdrawal state from other stimulants, including caffeine
A. The general criteria for withdrawal state (F1x.3) must be met
B. There is dysphoric mood (for instance, sadness or anhedonia)
C. Any two of the following signs must be present
(1) Lethargy and fatigue
(2) Psychomotor retardation or agitation
(3) Craving for stimulant drugs
(4) Increased appetite
(5) Insomnia or hypersomnia
(6) Bizarre or unpleasant dreams

From ICD-10 (2013)

inhibiting caffeine metabolism. Based on animal studies, the median lethal dose was estimated to be 192 mg/kg; when extrapolating to humans, this should correspond to an intake of around 10 g of caffeine, corresponding to 80–100 cups of coffee (Peters 1967), making the occurrence of overdose with regular coffee not very probable.

26.6 Chronic Risks of Caffeine Use

26.6.1 Caffeine Dependence and Addiction

"Caffeine dependence" and "caffeine abuse" are not included in the DSM-IV, even if these terms are frequently used in the lay and medical literature. In general there are not sufficient criteria to establish the diagnosis of caffeine dependence, even if 50 % of regular caffeine users will present with withdrawal symptoms in case of acute abstinence. As for caffeine intoxication, the caffeine withdrawal syndrome is included in both DSM and ICD classifications. The ICD-10 criteria for the caffeine withdrawal state (F15.3) are found in Table 26.2.

During the preparation of the new DSM5 classification discussions on the inclusion of caffeine dependence and/or withdrawal syndrome have taken place, but caffeine was not included as a DSM-5 substance abuse disorder (see www.dsm5.org).

The caffeine withdrawal syndrome is probably largely underdiagnosed. It can occur after sudden abstinence from regular caffeine even at rather low intake of 100 mg daily (Juliano and Griffiths 2004). The most frequent symptoms are headache, fatigue, decreased energy/activeness, decreased alertness, drowsiness, decreased contentedness, depressed mood, difficulty concentrating, irritability, and being foggy/not clearheaded. Symptoms occur after 12–24 h of abstinence and last for several days. The severity and duration of symptoms are related to the amount of regular caffeine intake. Juliano and Griffiths (2004) suggest that expectancies are not a prime determinant of caffeine withdrawal and that avoidance of withdrawal symptoms plays a central role in habitual caffeine consumption.

Patients who are hospitalized and depending on their state or inpatient regulations (decaffeinated coffee only in psychiatric settings) can find themselves in caffeine withdrawal with symptoms that can be misinterpreted or unrecognized. For instance, for a patient suffering from head trauma and not receiving his daily coffee, the severity of the headache can very well be influenced by the lack of caffeine.

The same misinterpretation can occur during expeditions at high altitude. For practical reasons or fear of increasing sleeplessness and risk of dehydration, caffeine intake is often stopped in this context. Several symptoms of altitude sickness and caffeine withdrawal are common, such as headache, fatigue, and lassitude (Hackett 2010). Hackett suggests that during expeditions caffeine likely will have more beneficial than negative effects, especially in regular coffee drinkers.

26.6.2 Other Chronic Risks

Heavy caffeine use is often associated with increased risk for use, misuse, or dependence on other substances or addictive behaviors. This correlation does absolutely not mean causality, but different studies suggest a two- to threefold increase of prevalence of tobacco dependence or problematic alcohol use for those

consuming more than 6–7 cups of coffee per day compared to those taking 1–2 cups (Greden 1992; Kabagambe 2013). The combined (and increasing) use of energy drinks with alcohol in adolescents and young adults deserves specific attention.

Caffeine can induce panic attacks in some individuals, but seems not be correlated to the occurrence of negative outcomes of chronic psychiatric problems. A link between heavy caffeine use and schizophrenic relapse has been suggested but not confirmed (Greden 1992).

Several studies suggest a correlation between high caffeine intake (>5 cups of coffee daily) and risk of lower bone density and increased risk of fracture, especially in lean elderly women and/or those having low calcium intake, but with tea intake correlated to higher bone density (Korpelainen 2003; Kagambe 2013).

The use of unfiltered coffee has been associated with increased level of cholesterol, a major risk factor for cardiovascular disease (Rodrigues 2003). Still, the effect of filtered and unfiltered coffee on other risk factors is not fully clear, and even if caffeine can induce tachycardia and arrhythmia, the available literature suggests that caffeine has more benefits than risks for cardiovascular disease.

The same seems to be true for the oncology field (see below).

26.7 Benefits of Methylxantine

26.7.1 Caffeine

As said before, when considering the benefits of caffeine, we remind that there is a difference between the benefits of caffeine itself and the benefits of coffee or other caffeine-containing drinks. Coffee contains hundreds of other compounds that are antioxidants (polyphenols, flavonoids, catechins, melanoidins, etc.) that pass through coffee filters.

Moreover, it is globally difficult to speak only of caffeine because only few publications are about caffeine itself. Most scientific evidence is related to studies on coffee and do not consider the biologic effect of caffeine. In energy drinks, the consequences of caffeine are difficult to isolate from those due to the high content of sugar and other components like vitamins or the amino acid taurine.

First of all, there are strong suggestions that taking caffeine from coffee is associated with a diminution of the risk of total or specific mortality (Freedman et al. 2012). This study is based on the follow-up of more than 229,000 men and 173,000 women for 13 years. At inclusion, participants' age varied between 50 and 71 years. After adjustment for tobacco-smoking status and other possible biases, the risk of death was inversely correlated to coffee consumption. The benefit became significant at one cup of coffee per day for men (hazard ratio 0.94, 95 % confidence interval 0.86–0.93) and at two or three cups of coffee for women (hazard ratio 0.87, 95 % confidence interval 0.83–0.92). The benefit tended to rise with the amount of coffee taken, with a statistical inverse correlation between caffeine and mortality. An inverse correlation was also observed for death from respiratory disease, injuries, diabetes, and infection. No association was found between caffeine and

cancer-related mortality. These results were confirmed in subgroups, including people in very good health at inclusion. In this study, the inverse correlation for heart disease and stroke was at the limit of statistical significance. Cardiovascular diseases will be discussed later in the chapter.

When searching specific potential benefits of coffee for several diseases, the most impressive observed effect is on liver disease. A large cohort study (Klastky et al. 2006) (more than 129,000 subjects) was conducted over 20 years, from the 1980s in the USA. A strong inverse correlation was found between cirrhosis and coffee drinking especially when the origin of the cirrhosis was alcohol. In this case, there was a 40 % risk reduction in 16-year cirrhosis incidence when people drank 1–3 cups of coffee (relative risk 0.6, 95 % confidence interval 0.4–0.8) and an 80 % risk reduction for four or more cups (relative risk 0.2, 95 % confidence interval 0.1–0.4). For nonalcoholic cirrhosis there was no significant risk reduction of caffeine on mortality and a nonsignificant 30 % risk reduction for people drinking four or more cups (relative risk 0.7, 95 % confidence interval 0.4–1.3). This relation was not observed for tea drinkers. Other cohort and case-control studies found strong reduction in the risk of liver cancer in coffee drinkers, with an increase in consumption of two cups of coffee per day being associated with a 43 % reduced risk of liver cancer (relative risk 0.57, 95 % confidence interval 0.49–0.67) (Larsson and Wolk 2007).

Coffee use is also inversely correlated to progression of fibrosis in hepatitis C liver disease (Freedman et al. 2009). This is important since the prevalence of hepatitis C is estimated to be at least 12 % in the addiction field, also among non-injecting drug users (Macias et al. 2008). The relative risk of two-point increase in fibrosis was 0.70 (0.48–1.02) for one or two cups of coffee a day and 0.47 (0.27–0.85) for three or more cups per day (significant trend). Although these are observational data (for evident ethical reasons, randomized studies will be difficult to realize), it is probable that people suffering from chronic hepatitis C are partially protected from fibrosis progression if they drink coffee on a regular basis.

Furthermore, the same authors found later that drinking coffee was a predictor to response to hepatitis C treatment with pegylated interferon and ribavirin (Freedman et al. 2011). The probability to achieve sustained virological response was almost twice for coffee drinkers of three or more cups of coffee daily (odds ratio 1.8, 95 % confidence interval 0.8–3.9).

Patients suffering from drug addiction (legal or illegal) have a higher prevalence cardiovascular risk factors and disease than the general population.

Tobacco smoking is more common in this population; one study suggests there is not a lower physical activity or unbalanced diet (Berg and Høstmark 1996), but this study included few and young participants (22-year-olds). Interventions promoting cardiovascular and heart health are important in the addicted population.

For the general population, caffeine consumption was considered to have a negative impact on the cardiovascular system until the 1990s. More recent studies suggest that coffee has no effect on the incidence of cardiovascular events and even suggest a small benefit for people without preexisting cardiac disease.

While people drinking coffee had a trend (at the limit of statistical significance) for beneficial cardiovascular effect in the first study discussed in this section

(Freedman et al. 2012), other studies have detected no association concerning men and a reduction in the cardiovascular mortality for women (relative risk of death 0.83, confidence interval 0.73–0.95) (Lopez-Garcia et al. 2008). For stroke, a 20 % reduction of relative risk has been found in a cohort study of women (Larsson et al. 2011); this was consistent with the results of another study concerning men (Larsson et al. 2008).

The effect of caffeine on insulin resistance is controversial and probably depends on the source of caffeine and the duration of exposition. At short term, caffeine has been shown to diminish insulin sensitivity (Beaudoin and Graham 2011). In a randomized controlled study, a dosage from 400 mg caffeine per day for a week showed a diminution of 35 % (95 % confidence interval 7–62 %) of insulin sensitivity (MacKenzie et al. 2007). In another study, sweet caffeinated beverages tended to increase type 2 diabetes (Malik et al. 2010). Still, it was not possible to separate the effect of sugar or caffeine. The long-term effect of pure caffeine from other sources than tea or coffee seems to have the opposite effect in animal models, ameliorating the insulin sensitivity and neutralizing the negative metabolic of sucrose in rats (Park et al. 2007). The limitations of this study are that it was conducted not in humans but in type I diabetic rats. In humans, the regular consumption of coffee has been clearly linked to decrease incidence of type 2 diabetes (Huxley et al. 2009). In this study, the relative risk was diminished by 7 % for any additional cup of coffee or tea absorbed. This effect was not associated with certainty to caffeine as it was also observed with decaffeinated coffee.

Caffeine also influences the metabolism of uric acid and occurrence of gout (Choi et al. 2007). In this large observational study, more than 50,000 men without former episode of gout were followed for 12 years. The relative risk of incidental gout was reduced by almost 60 % (relative risk 0.41, 95 % confidence interval 0.19–0.88) for the group consuming a large amount of coffee (six cups a day or more). The smallest efficient dose for gout protection was 4–5 cups of coffee a day with a 40 % risk reduction (relative risk 0.60, 95 % confidence interval 0.41–0.87). This was clearly linked to coffee and not caffeine, as this protective effect was not observed with tea or other sources of caffeine.

Tea and coffee (at a dosage of 300 mg caffeine per day) have been shown to protect against Parkinson disease, with a risk reduction of 25 % (relative risk 0.75, 95 % confidence interval 0.68–0.82) (Costa et al. 2010), excluding women taking hormonal replacement after menopause.

A neuroprotective effect of coffee on Alzheimer disease seems to exist, but this assumption is based on a small number of observational studies (Barranco Quintana 2007). The risk reduction could be 30 % (relative risk 0.7, 95 % confidence interval 0.55–0.9).

A recent case-control study in Australia confirmed the potential benefit of caffeine to prevent road accidents (Sharwood et al. 2013). More than 500 professional drivers involved in crash accidents were compared to controls. After adjustment for confounding factors, drivers who consumed caffeine (from coffee, tea, energy drinks, or tablets) had a risk reduction of 63 % of being involved in an accident (odds ratio 0.37, 95 % confidence interval 0.27–0.50). This is probably due to the psychostimulant properties of caffeine (increase alertness, lessen fatigue, promote memory, prevent

errors to people who are tired or working on night shift (Ker 2010). Also in light drinkers, the accident reduction was found; this is an argument against that it was only an effect of the reversal of withdrawal (Childs and de Wit 2006).

Another well-established positive effect from caffeine is the enhancement of physical capacities (Burke 2008). The most effective dosage for this purpose seems to be around 3 mg caffeine per kilogram of weight. Positive impact was found on intermittent effort sports (e.g., soccer), continued effort sports lasting until 1 h (e.g., swimming), or endurance sports (e.g., running). The enhancing effect of caffeine is so significant that for a long time, caffeine was considered a doping substance controlled by the World Anti-doping Agency (WADA). In 2004 caffeine was removed from the list (www.wada-ama.org).

The potential analgesic properties of caffeine are subject of debate. Caffeine is successfully used in the treatment of headache or migraine (Goldstein et al. 2006) and is a frequent component of combined analgesics or other medication (e.g., when mixed with paracetamol or salicylates or antihistamines). On the other hand, it can be the cause of headache (Bigal et al. 2002). This phenomenon can take place when people chronically consume caffeine or in withdrawal conditions.

Coffee and tea also seem to present benefit for mental health based on a data of a large cohort from the Nurses' Health Study. More than 50,000 women not suffering from depression at baseline were followed for 10 years, between 1996 and 2006, and stratified by their consumption of caffeine (Lucas et al. 2011). During the follow-up, a 20 % risk reduction for depression was found for women consuming 550 mg of caffeine or more when compared to the group consuming 100 mg or less (multivariate relative risk 0.80, 95 % confidence interval 0.68–0.95). This effect is quite clearly related to caffeine itself as it was not observed for women drinking decaffeinated coffee. Such results are coherent with data from other studies showing an inverse correlation between coffee, depression, and suicide (Kawachi et al. 1996).

26.7.2 Theophylline

Theophylline, another methylxanthine (1,3-dimethylxanthine), is found in medication form and in small quantity in tea, coffee, chocolate, mate, and guarana. Its principal indications are related to its bronchodilatative properties and immunomodulatory effects (Somerville 2001). It is known to restore the sensitivity to corticosteroids in asthma. Consequently theophylline is used in asthma and chronic obstructive pulmonary disease. It seems that it could also be useful for the prevention of acute kidney injury caused by radiologic contrast product (Dai et al. 2012). It is not as psychoactive as caffeine and not known to be a substance of abuse.

26.7.3 Theobromine

There is a popular belief that theobromine, a third methylxanthine, found principally in guarana, cacao, and chocolate, has a euphoric effect, but no studies can

confirm this. The appetite for chocolate would be more linked to other methylxanthine such as caffeine and taste or cultural influences. So up to know, there are no proven benefits for theobromine (Smith 2011).

26.7.4 Caffeine Abuse Treatment

In case of acute intoxication (Yew and Laczek 2011), which necessitates more than 70 mg/kg (Bronstein et al. 2010), clinical management should be "supportive." The first action is to give standard protocols for cardiac life or other support (ABCs) (Pohler 2010). Then give oxygen to the patient and check the blood glucose. In case of extreme anxiety, agitation, or seizure and lack of effect of non-pharmacological interventions, give short-acting benzodiazepines (e.g., lorazepam orally when possible or intravenously/intramuscularly).

Activated charcoal is effective in reducing the absorption of methylxanthine and recommended early in the treatment. Then transfer the patient to an emergency unit where the care will be supportive, depending on the symptoms. Cardiovascular or neurologic toxicities are the most frequent. Sinus tachycardia occurs but does, in general, not require any intervention, but arrhythmia does. In case of extremely high caffeine levels, a dialysis or hemofiltration may be necessary.

Gastric lavage is rarely done because of aspiration risk. Caffeine is rapidly absorbed, and gastric lavage should not be considered unless in the first hour after intake.

In case of withdrawal, no specific treatment or intervention was found in scientific publications. Anyway, caffeine withdrawal is not dangerous and self-limited. Intervention would then not be crucial. A wait-and-see approach could be used. Nevertheless, the main problems during caffeine withdrawal could be fatigue, lack of concentration, or headache. We can recommend general interventions such as rest, physical activity, and good fluid and electrolyte supply. In case of severe headaches, simple analgesia (e.g., paracetamol) could be used. If the time to go through withdrawal is really not adequate, for example, in case of professional or familial obligations, caffeine (in a limited dose) could be taken in the form of coffee, a caffeine-containing drink, or a tablet, and complete withdrawal conducted later. For regular caffeine users who will be exposed to a period of caffeine abstinence (e.g., planned medical intervention), a decrease of daily caffeine intake days before is recommended (Favrod-Coune and Broers 2010).

26.8 International Perspectives

Currently, coffee, tea, and other caffeine-containing drinks are legally available in all countries and not subjected to regulation. Based on our review of benefits and risks of methylxanthines, we believe that there is no rationale to change this. This seems neither necessary nor useful in a public health or cultural perspective, as prohibition certainly will have a number of unwanted side effects. Nevertheless,

information and warning (on package of food or drinks) are probably warranted, indicating the risk of high doses of caffeine and when mixed with alcohol and when relevant the risk of sugar, calories, or other compounds.

The FDA has warned four companies about adding caffeine to alcoholic beverages in 2010 (Herndon 2010) and stated that a further action, including the seizure of products, is possible under federal law. The FDA stated that caffeine is an "unsafe food additive" when mixed with alcohol.

Another international measure that we consider useful would be a limitation of the amount of caffeine in energy drinks. It seems difficult to reach toxic levels of caffeine when a drink contains 50–100 mg of caffeine. Nevertheless, content of 500 mg caffeine in one drink can represent a real danger, especially for children or teenagers, given their lower body weight and the propensity to like those drinks.

26.9 Conclusion

Safe caffeine use is possible and moderate caffeine use (200–300 mg per day) probably has more benefits than risks. Relative contraindications for caffeine intake are uncompensated heart disease, anxiety, and sleeping problems. Since most studies on caffeine use are observational, we can of course not recommend the use of caffeine or other methylxanthines for medical reasons to those who do not drink. The studies are merely based on cohorts of individuals drinking coffee and tea, so we should recommend the use of these beverages and not of energy drinks. Energy drinks lack several compounds found in coffee or tea (antioxidants) and contain others that possibly have a negative impact on health (sugar). In case of liver disease, especially if related to alcohol and HCV, a daily intake of at least five cups of coffee can be recommended to diminish the progression of the disease.

Coffee and caffeine withdrawal symptoms exist and are often not recognized, especially in treatment settings, where caffeine withdrawal can be confounded with other symptoms. Caffeine withdrawal occurs in half of regular coffee drinkers, even at moderate caffeine intake. The most common symptoms are headache, fatigue, and difficulty to concentrate. Health professionals and patients should be better informed about these symptoms and the risk of occurrence of caffeine withdrawal.

Caffeine intoxication and withdrawal are recognized clinical entities, but caffeine dependence is currently not. Some individuals can meet difficulties in controlling their caffeine intake and present withdrawal symptoms in case of abstinence, but most often other criteria of dependence are lacking. In some cases such behavior seems close to an obsessive-compulsive or eating disorder.

In psychiatric inpatient settings, often only decaffeinated coffee is available. We recommend, for the reasons mentioned above, that both caffeinated and decaffeinated coffee be at the disposition of the patients, with restriction for those who suffer from anxiety or insomnia. Caffeine taken from coffee seems to be without risk for most psychiatric patients. Personalized recommendations (maximum daily quantity of caffeine, time limit) are probably more appropriate than constraining all patients to abstain from coffee consumption.

Finally, we highly recommend more and better information to the population about the risk of acute intoxication of caffeine, the nutritional and metabolic risks of energy drinks, and the problems of mixing these with alcohol. Warning messages on caffeine-containing food or drinks as well as a legal limitation of the content of caffeine (e.g., maximum 200 mg per unit) are certainly justified. They should be promoted in all countries.

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Khat Addiction

27

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Contents

Abstract

Khat refers to the young and tender leaves and shoots of the khat tree (*Catha edulis*). It is an evergreen tree that can be found in the Abyssinian highlands, the Horn of Africa, Eastern and Southern Africa, the Arab peninsula, and Afghanistan.

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The alkaloid cathinone (S-(-)-a-aminopropiophenone) is considered to be the main psychoactive compound. The leaves and tender stems are usually chewed and kept in a tight wad in the cheek pocket. Within about 15–30 min, the user experiences physiological excitability, euphoria, talkativeness, and flow of ideas. Today, cathinone is listed in Schedule I and cathine in Schedule III of the international Convention on Psychotropic Substances of 1971, but the khat leaves are not internationally controlled. A problem with diagnosis of khat addiction is that established dependence criteria are not easily applicable as is the case for other traditional substances. More research information is needed about the prevalence of a khat dependence, its consequences, and its treatment.

27.1 Introduction

Khat refers to the young and tender leaves and shoots of the khat tree (*Catha edulis*). It is an evergreen tree of the *Celastraceae* family, normally reaching 6 m in height, but in an equatorial climate it might grow to 25 m. *Catha edulis* can be found in the Abyssinian highlands, the Horn of Africa, Eastern and Southern Africa, the Arab peninsula, and Afghanistan. Khat has many names including *qat* (Yemen), *jad*/*chat* (Ethiopia, Somalia), *miraa* (Kenya), or *marungi* (Uganda, Rwanda).

The khat leaves have been consumed for centuries for their mildly stimulating properties caused by several alkaloids contained in the leaves. Among more than 40 known compounds, the alkaloid cathinone (S-(-)-a-aminopropiophenone) is considered to be the main psychoactive compound, but it is unstable and swiftly decomposes after harvesting. Cathinone resembles amphetamine in chemical structure and affects the central and peripheral nervous system and behavior similarly (Kalix 1990). Recently, synthetic cathinone derivates such as mephedrone have been introduced to the drug market, often under the label "legal highs" (EMCDDA 2012). More stable compounds of the khat leaves are cathine (*S*,*S*-(+)-norpseudoephedrine) and other alkaloids which are at the same time metabolites of cathinone and less potent central and peripheral stimulants.

While chewing the fresh leaves has ever since been the preferred use form, in the past it was often only available in dried form, powder or paste. Today, soon after harvesting, the twigs and shoots are artfully rolled into bundles and wrapped into banana leaves in order to retain moisture; today, deep frozen transports are more and more common. In most instances, bundles are the traded units, but leaves of lower quality might also be marketed in standardized plastic bags. The leaves and tender stems are usually chewed and kept in a tight wad in the cheek pocket. Within about 15–30 min the user experiences physiological excitability, euphoria, talkativeness, and flow of ideas known in Arabic as "mirquaan." This is followed by a quieter, more introvert phase, giving way to a gradual comedown, and among excessive chewers often restlessness, irritability, and depressive reaction. Users often experience sleep problems during the following night and a hangover the next morning. These unpleasant aftereffects motivate some khat chewers to carry on chewing without stopping.

27.2 The Khat Controversy

The controversy around khat and especially the question whether it is a *drug* versus a part of *culture* or *tradition* is probably as old as use itself (Krikorian 1984). It has been condemned by the Ethiopian orthodox church and the more fundamentalist Islamic schools of thought particularly in Saudi Arabia, who consider it "haram." Islamic scholars in Yemen, Somalia, and Ethiopia by contrast integrated khat use into religious life, including the study of the Holy Koran or to enhance religious experience as practiced by Sufi mystics. During the colonial era, arguments about moral degeneration, falling economic productivity, and the association with political unrest motivated official and largely unsuccessful bans on khat (Gatter 2012; Warfa et al. 2007). Strong pro-khat movements prevented in most countries legal restrictions.

The scientific discourse on khat shows similar fissures, usually along the lines of academic discipline (Odenwald et al. 2010a). Medical and pharmacological research approached khat with the underlying assumption that it is analogous to other psychoactive drugs; consequently, research focused on the discovery of the addictive substance in the leaves and on the laboratory-based study of cathinone. Today, cathinone is listed in Schedule I and cathine in Schedule III of the international Convention on Psychotropic Substances of 1971, but the khat leaves are not internationally controlled.

Anthropologists and social scientists, by contrast, stressed the cultural functions and traditional values (Anderson et al. 2007). They often oppose the medical position, e.g., arguing that the physical effects cannot explain the functions of its use and that addiction is a western concept that does not fully grasp the case of khat.

27.3 The History of Khat Use

Medieval writings and legends confirm its longstanding use but also ambivalent attitudes towards its effects described as helpful and joyful as well as noxious (Krikorian 1984). Before the eighteenth century, its use was confided to certain ethnic groups and producing areas where khat was an integral part of the culture, i.e., religious ceremonies and rites of passage, but there only the rich and the farmers themselves were regular chewers. The former used khat to get inspiration for artistic expression in poetry and songs, chewed communally, in dedicated rooms within private households often called "mafrishes." The latter as well as long-distance travelers used khat to overcome tiredness and hunger. But it was also chewed during Muslim prayers and ceremonies as well as by students to be able to study all night. The traditionally moderating khat culture regulated its use and prevented large-scale misuse by rules such as restriction to afternoon and evening hours and weekends as well as rites of passage. Outside the few traditional producing areas, it was very rare, e.g., for medicinal purposes, and not noticed by European travelers before the Swedish botanist Peter Forsskål (1732–1763). Since then, its use became more and more prevalent and by the year 1900 the "khat party"

has emerged as a central social institution of the respective regional populations, especially in Yemen: a controlled, formalized, and exclusive group setting of adult males where politics and business are discussed and social status was demonstrated (Weir 1985). Since then, khat chewing has successively become a regular part of social life outside these confined groups and regions, and the moderating khat culture is gradually being lost.

27.4 From a Niche Crop to a Cash Crop

Since the end of the nineteenth century with successive transport innovations, the railway network, road haulage, and air cargo, khat has made its way from a niche crop to a cash crop. For commercial purposes, nowadays, it is grown in the highlands around the Horn of Africa, Southern Arabia, and along the Eastern African coast in altitudes of 1,500–2,500 m above sea level. Within centuries, an amazing variety of khat types have developed out of regional climatic and environmental conditions and local cultivation habits which has been the base for the recent marketing of different khat brands. After decades of steeply increasing production, now the khat sector has economic significance for Ethiopia and Yemen and to a smaller extent for Kenya too, where it provides more than two million jobs, for farmer, pickers, packers, and traders, i.e., the source of income for up to 15 million (Anderson et al. 2007; Gatter 2012). Within a few decades, khat has become a large regional and international market without the involvement of multinationals. Today, production is rising in traditional khat countries, while at the same time expanding to other African countries (e.g., Uganda, Rwanda). But the production increase and the accompanying development have considerably contributed to environmental and social problems, e.g., deforestation and food insecurity in Ethiopia or groundwater decline due to massive increase of irrigation farming in Yemen (Gatter 2012).

27.5 The Development from Traditional to Binge Use Patterns

Estimating the prevalence of khat use is difficult, as the consumption in the different countries still largely depends on socioeconomic, ethnic, and geographic factors. The current literature is a patchwork of different studies produced with different methods. The general trend suggests use is spreading across the general population, including groups who have no tradition of khat consumption. This includes countries where it was previously unknown altogether. It is estimated that more than ten million people are using khat recreationally on any one day (Odenwald et al. 2010a).

In Yemen different prevalence estimates vary between 60 % and 90 % of adult males and between 10 % and 50 % of adult women. Different Household Budget Surveys indicated that Yemenite households spent on average 9–10 % of their income on buying khat, but this proportion was up to 40 % in the lowest income section (Gatter 2012).

In Ethiopia, different studies found prevalence estimates between 40 % and 75 % among adult males and between 16 % and 35 % among adult women (e.g., Alemseged et al. 2012). A representative national assessment of 16,606 adolescents and young adults found a 4-week prevalence of 16.2 % (Kebede et al. 2005). Other studies among Ethiopian high school or university students revealed current prevalence rates of 10–65 %. All studies revealed great differences between urban and rural areas as well as between different ethnic groups.

In Kenya, no prevalence data for the general population are available. Studies of treatment-seeking patients in different parts of the country disclosed a lifetime prevalence rate of 10.7 % in a region without khat production (Othieno et al. 2000) and a current prevalence rate of approximately 30 % in a khat-producing region (Ndetei et al. 2009).

Cross-sectional assessments of khat use in Somalia reported regular or current khat use between 31 % and 64 % of adult males in the north of the country and 21 % in the south, and excessive khat use patterns were especially found among militia members (Elmi 1983; Odenwald et al. 2005).

Other countries where khat is traditionally used include Djibouti, Saudi Arabia, Tanzania, Madagascar, and South Africa. Because of mass migration, khat use spread to the European Community, North America, Australia, and Israel. Khat use in western countries is almost exclusively limited to immigrant groups. Among Somalis in the UK, a lifetime history of khat use was found among 38–78 % (58–79 % of males, 16–76 % of females), and current use was found among 34–67 % of males and 17 % of females (e.g., Bhui and Warfa 2010).

The pattern of khat use has changed significantly over recent decades due in part to the combined effects of urbanization, commodification, and the accompanying social change (Anderson et al. 2007). Arguably, the dissolution of traditional, formal regulations has led to the rise of more excessive and extensive khat use, including "binge sessions" of lasting more than 24 h in a row, use in the morning as eye opener, and parallel use of other drugs, e.g., benzodiazepines or alcohol (Odenwald et al. 2010b). While khat chewers used to be traditionally "initiated" at around 20 years of age, nowadays, they start using the drug as early as 8 years in life and consumption has become part of the youth culture (Odenwald et al. 2010b). Furthermore, what was reportedly an exclusively male habit is now practiced more and more by women, including at times during pregnancy and breastfeeding (Odenwald et al. 2010b).

27.6 What Is Known About Khat Addiction?

The compulsive use of the khat leaves has been described since colonial times (Halbach 1972). Compared to other substances with misuse potential, experts consider the khat leaves, however, to have a low potential for addiction and physical and social harms (Nutt et al. 2007), and they are not recommended to be scheduled or controlled under the international conventions (World Health Organization 2006). In some countries, however, they are illegal, in others the status is not clear, while they are not controlled at all in the traditional khat

countries (Griffiths et al. 2010). While the khat leaves are considered to produce only mild psychological addiction, cathinone is believed to have a higher addiction potential than amphetamine (Kalix 1991).

The current opinion on withdrawal symptoms upon discontinuation is that they are expected to be mild, to be brief, and to occur only after prolonged use (World Health Organization 2006) and include profound lassitude; anergia; difficulty in initiating normal activity; slight trembling lasting for several days after cessation; and nightmares, often paranoid in nature, for example, being attacked, strangled, or followed (e.g., Kennedy et al. 1980). However, the existing empirical base is meager and not related to current excessive use patterns.

In the same token, today it is generally believed that khat use does induce some tolerance (World Health Organization 2006). It has been argued that the chewing mode of ingestion limits the possible amount to consume in a certain time and, thus, tolerance development is usually prevented. This view can be criticized based on recent definitions of tolerance. Among stimulant users, tolerance development, the upward shift in the set point for reward, and the subsequent dysphoria ("opponent process") are closely related to the development of "binge" consumption patterns: Users need to increase the dose and the frequency of drug administration in order to experience the desired psychological effects. Thus, khat tolerance development might not only include increases in the amount of consumption per time unit but rather the extension of the time spent for consuming it which leads to an increase of the absolute amount ingested. Recent studies and personal observations indicate that a growing group of binge users consume khat for more than 24 h in a row in such large quantities a novice would never manage (Patel et al. 2005; Nabuzoka and Badhadhe 2000; Widmann 2012). While the development of tolerance to physiological effects was reported (Nencini et al. 1984), no study has ever directly targeted the topic of tolerance to desired psychological effects, e.g., euphoria.

Researchers early on recognized the potential of khat to induce psychological dependence (e.g., Kennedy et al. 1980). This is best illustrated in descriptions of typical scenes of inner city khat markets at the Horn of Africa or in Eastern Africa at the time just before a khat delivery arrives (Hansen 2010). At theses hours of day, users speed to khat markets frequently causing traffic accidents; an aggressive and nervous atmosphere prevails until the khat trucks arrive. In contrast, khat users who visit foreign countries are said to abstain without any difficulties without replacement.

Observational data confirm the existence of a specific Patois among Somali khat users (Odenwald et al. 2010b): "xaraaro" means feelings of craving and nervousness which are experienced by habitual chewers at the time of day before their usual khat intake starts; "dubaab", i.e. nightmares involving the sensation of being suffocated, are usually experienced by heavy chewers in the first days after cessation. The phenomenon of "jibane" involves the use of khat in a group setting in order to reduce aversive symptoms in the morning. The term "bac," which literally means "plastic bag," refers to a transitory phenomenon involving paranoid anxiety and illusions when khat users on their way home at night mistake litter on the street for enemies or dangerous animals.

In recent years khat has increasingly been used in combination with other substances like alcohol or benzodiazepines. Khat chewers usually smoke tobacco during khat sessions and consume carbonated soft drinks; this goes so far that it is difficult to find any khat chewer who doesn't smoke. Inversely, there are many occasional smokers that do only smoke during khat sessions (al'Absi and Grabowski 2012). In a recent study, khat chewers used more tobacco, khat dependence correlated with tobacco dependence, and there were signs of an enhancement effect (Kassim et al. 2011).

27.7 Measurement and Diagnosis of Khat Addiction

A problem with diagnosis of khat addiction is that established dependence criteria are not easily applicable as is the case for other traditional substances. Besides the previously mentioned lack of knowledge on withdrawal and tolerance, some of the other criteria outlined in DSM-IV (or ICD-10 research criteria) need further specification to adapt to societies where daily social khat use is rather the rule than the exception and where social khat use is the most widely used leisure activity, i.e., "a great deal of time is spent in activities necessary to get drugs (e.g., visiting multiple doctors, driving long distances), using drugs, or recovering from its effects" or "important social, occupational, or recreational activities given up or reduced because of drug use." It needs studies and/or conventions that set the borders of what is normal and what is socially not sanctioned any more.

Consequently, less information is available from cross-sectional studies on the prevalence of a khat dependence syndrome as defined by the simple application of ICD or DSM criteria. An Ethiopian study (Awas et al. 1999), using the WHO's Composite International Diagnostic Interview, found a prevalence of khat dependence according to the criteria of ICD-10 of 5 % among males (among females 1.3 %) in a representative sample drawn in a traditional khat-producing area. Using the same instrument among a group of 25 chronic psychotic patients in Somalia revealed a percentage of 84 % (Odenwald et al. 2012). Using the criteria as outlined in the Mini International Neuropsychiatric Interview, 100 % among 33 khat-using male Somali refugees in Nairobi (Widmann 2012) had to be considered dependent. All of these studies developed their own conventions to adapt dependence criteria to the reality of khat use.

Validated self-report instruments to assess and measure aspects of khat addiction are rare and few standardized questionnaires have ever been applied in khat users. Recently, an Arab version of the Severity of Dependence Scale, a five-item instrument thought to measure the psychological component of dependence, has been adapted and validated for the study of khat addiction (Kassim et al. 2010). It was shown that khat chewers scoring high on this instrument show more khat-related behaviors and have higher khat alkaloid levels in their saliva (Kassim et al. 2012). In different studies, 10–39 % of khat users scored at a level comparable with a clinical population with severe heroin dependence in need for treatment (Kassim and Croucher 2006). A Somali version of this instrument has also been developed (Odenwald et al. 2012).

27.8 Khat-Associated Neurocognitive Deficits

A common characteristic of chronic central stimulant abuse is marked neurocognitive deficits. A recent review found that there is only one study on neurocognitive deficits among khat users before 2009 (Hoffman and al'Absi 2010). Khattab and Amer (1995) assessed aircrew members of an Arabic Airline who were daily khat chewers (25), occasional chewers (39), and non-chewers (24) presented for the Standard Aviation Medical Examination and participated in a standardized neuropsychological test battery. Daily khat chewers performed worst in subtests for perceptual speed, long-term memory, visual memory, and visual perception and had a faster EEG background activity compared to occasional khat chewers and non-chewers. Duration and amount of khat use were negatively correlated with performance. Recently, several studies found poorer working memory among severe khat users compared to controls (Hoffman and al'Absi 2012; Colzato et al. 2011; Mikulica 2012). Other studies reported different other executive functions being impaired among khat users: inhibitory control (Colzato et al. 2010), problem solving (Mikulica 2012), cognitive flexibility (Colzato et al. 2011), cognitive control (Colzato et al. 2012), and processing speed (Hoffman and al'Absi 2012).

27.9 Treatment of Khat Addiction

The UNODC's annual World Drug Reports list khat in the statistics of "primary substances of abuse". According to these reports, khat-addicted individuals constitute the largest group in Ethiopia and the second largest group in Kenya (United Nations Office on Drugs and Crime 2012). However, the UNODC statistics have to be treated with caution as they reflect the reporting of governmental statistics to the UN and as the absolute numbers of provided treatments is very small in these countries. But single research reports verify the existence of this group of patients not just in the countries mentioned above but also in Uganda. Khat-dependent individuals who seek treatment are usually admitted to psychiatric and general substance treatment units. But the number of cases is small and the psychiatric and addiction treatment facilities in this region of the world are few. Specialized khat addiction programs or treatment facilities are nonexistent. Studies from these countries describing the development or evaluation of khat addiction treatment are lacking. But khat users in the traditional khat countries frequently report motivation to and failed attempts to quit its use (Odenwald et al. 2012). We reported before the observation that during the last 12 years, various local nongovernmental organizations in Ethiopia, Somalia, Kenya, and Uganda have started to address khat addiction as shown by many hand-painted billboards in Somali towns promoting "khat counseling" together with other psychosocial services such as "HIV counseling" (Odenwald et al. 2007). This reflects the demand for khat-related treatment in the traditional khat countries. However, no studies exist that addressed this counseling approach.

In western countries, khat addiction has been targeted by projects in the UK, Denmark, and Sweden. While some of the projects included khat addicts into the general addiction treatment settings, i.e., together with people dependent on other types of substances, others developed programs specifically for homogeneous ethnic subgroups, mostly Somalis. Observations from these projects confirm that patients with khat addiction usually are immigrants from the traditional khat countries, that utilization is poor, and that those who utilize these treatment facilities have comorbid other substance-related and psychiatric problems. Recently, khat addiction treatment has been included into web-based advertisements of private substance treatment centers; among a range of different explanations, this might suggest that there is a certain demand for this kind of treatment. Scientific publications from western countries on khat addiction treatment are missing. Systematic research on medication to treat khat addiction is equally nonexistent. There are only a few reports that mentioned the use and effect of certain psychopharmacological drugs in single cases.

27.10 Other Psychiatric Disorders and Somatic Problems Associated with Khat Use

Khat use has been associated to the presence of mental distress or disorders (Belew et al. 2000). While there is no evidence for a simple causal relationship or a noxious effect of khat use per se (Warfa et al. 2007), functional substance use to counteract symptoms of depression, posttraumatic stress disorder, as well as medication side effects have been described (Teferra et al. 2011). In these individuals, khat use may be a risk factor for the development of suicidal thoughts (Bhui et al. 2003) and psychotic symptoms (Odenwald et al. 2009). Today, more than 20 case descriptions of khat-induced brief psychotic episodes are available in the medical literature. Most reported excessive khat use before the onset of psychotic symptoms and violent behavior in the course of the acute psychiatric development. Most of them had completely remitted after 2–4 weeks, given abstinence is maintained even without medication. But, most of these cases had repeated such episodes. Also the exacerbation of psychotic symptoms in patients with preexisting psychotic disorders has been reported (Bimerew et al. 2007; Teferra et al. 2011). A few and weak studies found first support in favor of the hypothesis that early, chronic and severe khat use might be a causal factor for the development of chronic psychotic disorders (Odenwald et al. 2005).

Besides psychiatric sequelae, numerous somatic health problems have been associated with khat use (Al-Motarreb et al. 2010; for detailed review see Al-Habori 2005). As with mental health, moderate khat use seems not to be noxious in most users and adverse effects are commonly linked with the currently growing excessive use. There are many reports of severe physical harms among chronic users, but other explanations have not been systematically ruled out, for example, tobacco smoking which is frequently combined with *khat* use and pesticide content in the leaves. Observed negative somatic consequences associated to khat use

include mucosal problems, hypertension, cardiovascular complications, duodenal ulcers, sexual dysfunction, hepatoxicity, and reduced birth weight of infants born to *khat*-chewing mothers. By the same token, the argument for possible medicinal uses has only been touched on.

27.11 Conclusion

In sum, the topic of khat addiction urgently needs further empirical studies. Current evidence supports the hypothesis that excessive and prolonged khat use can produce a dependence and neurocognitive deficit syndrome qualitatively similar to that produced by amphetamine. But the question of khat-related withdrawal and tolerance needs further studying, especially related to current binge use patterns. For the application of diagnostic criteria to khat, conventions are needed as well as the development of reliable and valid research instruments. The current knowledge on khat addiction treatment is very poor especially as khat users seldom utilize addiction treatment services. It is urgently needed to develop effective and adequate treatment concepts to be applied in the traditional khat use countries and among immigrant communities elsewhere in the world; there are millions of people who potentially benefit from such knowledge. Like amphetamines khat can be associated to psychosis and other psychological and somatic disorders. Therefore, strong research designs are needed to rule out alternative explanations and develop public health strategies.

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Opioid Addiction: Short- and Long-Acting Opioids

28

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Contents

Abstract

Opium is the natural product obtained from the juice of the opium poppy (*Papaver somniferum*). Opiates include all natural plant alkaloids, such as morphine, codeine, and thebaine, and many semisynthetic derivatives. An opioid is any compound, regardless of the structure, which has the functional and pharmacological properties of an opiate. Endogenous opioids are natural ligands for opioid

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receptors found in animals. Synthetic compounds include hydrocodone; oxycodone; hydromorphone; heroin; antagonists such as naloxone, naltrexone, and nalmefene; and partial agonists such as buprenorphine. Opioid use disorders are a public health problem worldwide. They include intoxication, withdrawal, and dependence. Intoxication is the main cause of mortality of these disorders and can be treated with the opioid antagonist naloxone. Opioid withdrawal can be treated with opioid agonist such as methadone, buprenorphine, or LAAM. A depot formulation of naltrexone is approved to prevent a relapse prevention intervention. Research studies are underway with the goal of discovering and developing safer and more effective medications to treat these disorders.

28.1 Introduction

The objective of this chapter is to review the pharmacological (pharmacodynamics and pharmacokinetic) aspects of exogenous opioids involved in opioid-related disorders. The pharmacological treatment of opioid overdoses, opioid withdrawal, and opioid addiction including psychosocial therapy is also reviewed.

28.2 Opioids: Pharmacology and Treatment

28.2.1 Pharmacology of Opioids and Endogenous Opioid System

Opium is the natural product obtained from the juice of the opium poppy (*Papaver somniferum*). Opiates include all natural plant alkaloids, such as morphine, codeine, and thebaine, and many semisynthetic derivatives. An opioid is any compound, regardless of the structure, which has the functional and pharmacological properties of an opiate. Endogenous opioids are natural ligands for opioid receptors found in animals. Synthetic compounds include hydrocodone; oxycodone; hydromorphone; heroin; antagonists such as naloxone, naltrexone, and nalmefene; and partial agonists such as buprenorphine (Yaksh and Wallace 2011).

Opiates and opioids act on three opioid receptors (mu, kappa, and delta) which are widely distributed in the brain and are associated with reward stimuli (Kristensen et al. 1995). Endogenous opioids, called endorphins, are the ligands of these receptors and play a central role in establishing habits and responses for survival and pain relief; the opioid endogenous system plays an important role in opioid addiction (Mayer and Hollt 2006), and also it has been implicated in the pathophysiology of dependence of alcohol and cocaine (Kreek et al. 2009). The three opioid receptors belong to G protein receptor family, and its structure has an extracellular N-terminus, seven transmembrane domains, three extra- and intracellular loops, and an intracellular C-terminus. Agonist binding to these receptors results in conformational changes of the receptor and the activation of the G protein cycle, affecting the intracellular effectors: adenylate cyclases and Ca^{2+}/K^{+} ion channels. The final effect in the cell is the reduction of cAMP levels, the inhibition of the Ca^{2+} current, and the increase in the

Table 28.1 Classification of pharmacological opioid ligands based on its affinity for the opioid receptors (μ, δ, κ)

	Mu	Delta	Kappa	Others
Morphine	Ag+++	Ag+	Ag+	
Diacetylmorphine	Ag+++	Ag+	Ag+	
Methadone	Ag+++	Ag+	Ag++	NMDA antagonist
Codeine	Ag++			
Buprenorphine	PA	An+++	An++	
Oxycodone	Ag+++			
Hydromorphone	Ag+++		Ag+	
Hydrocodone	Ag+++			
Meperidine (pethidine)	Ag+++	Ag+	Ag+	Serotonergic activity
Pentazocine	An+	Ag+	Ag+	
LAAM	Ag+++			
Tramadol	Ag+			Norepinephric and serotonergic activity
Tapentadol	Ag+			Norepinephric activity
Naloxone	An+++	An+	An++	
Naltrexone	An+++	An+	An+++	
Nalmefene	An+++	An+	An++	

The number of symbols "+" is an indication of potency
Ag agonist, *PA* partial agonist, *An* antagonist

extracellular K^+ current. These changes tend to decrease the excitation of the neuron and inhibit the neurotransmission. Depending on the capacity to promote changes in the G protein, ligands are classified into full opioid agonists, partial agonists, antagonists, and agonists–antagonists (Table 28.1) (Schäfer 2011).

- An **agonist** is a substance that is capable of binding to a receptor, producing their activation and causing a biochemical or cellular response.
- An **antagonist** is the opposite of an agonist in the sense that as an antagonist it also binds to a receptor, but does not activate the receptor and blocks its activation by agonists.
- A **partial agonist** activates the receptor, but does not cause much effect as a full agonist, and has a ceiling of maxim effect inferior than the agonist.

28.2.1.1 Opioid Classification

Exogenous opioids can be classified according to their origin (natural, semisynthetic, and synthetic), their chemical structure, and/or their affinity/efficiency on opioid receptors. The latter is most often used, in which exogenous opioid drugs are divided into:

- **Pure agonist:** opioid agonists, receptor mu fundamentally, with high efficacy (intrinsic activity). This is the group of morphine, heroin, pethidine, methadone, fentanyl, and its derivatives.
- **Mixed agonist–antagonists**: act as agonists in one receptor (kappa) and as partial agonists or antagonists in another (mu). When administered together with a pure mu agonist, it may antagonize the effects and may reduce or

eliminate their analgesic effect. In opioid-dependent subjects, agonists (heroin) cause withdrawal symptoms. This is the group of pentazocine, butorphanol, or nalorphine.

- **Partial agonists**: act on mu receptors with lower efficacy than pure agonists. They are analgesic when administered alone but antagonize the effects of a pure agonist. The most characteristic of this group is buprenorphine.
- **Pure antagonists**: possess affinity for the receptors but not exhibit efficacy. Inhibit or reverse the action of the agonists and do not have analgesic effects. In subjects with opioid dependence, withdrawal symptoms occur. They are used in cases of poisoning or overdose by its ability to reverse the effects of exogenous opioids. They are naloxone and naltrexone.

28.2.1.2 Morphine

Morphine is a natural product of the seeds of the poppy plant. Chemically, morphine is an alkaloid that belongs to the class of phenanthrenes. Morphine is prescribed primarily as a high-potency analgesic. Morphine is metabolized by glucuronide conjugation to morphine-6-glucuronide (M6G) and morphine-3-glucuronide. M6G has mu receptor agonist activity and is approximately twice as potent as morphine in humans. In chronic administrations, M6G has a significant portion of the analgesic actions of morphine, and its plasma concentration exceeds those of morphine.

During the last years, slow-release oral morphine (SROM) has been proposed as an alternative maintenance pharmacotherapy for treatment of opioid dependence with retention rates similar to methadone (from 80.6 % to 95 %); also, uncontrolled studies showed improvements in quality of life, withdrawal symptoms, craving, and additional drug consumption (Jegu et al. 2011).

Pharmacodynamics

Morphine is the prototype for opioid agonist actions. Morphine is a selective agonist at the mu-opioid receptor at lower doses. There are described central and peripheral actions.

The main central actions are:

(a) **Sedation**: at higher doses, it could produce stupor, sleep, and coma. It worsens the psychomotor performance. At very high doses, convulsions can appear.
(b) **Euphoria**: it produces euphoria, pleasure, and a well-being feeling and reduces anxiety. The euphoria has been linked to the abuse potential of opioids.
(c) **Analgesia**: morphine can reduce the sensorial and affective components of pain. It can relieve and suppress acute and chronic pain. This action is related with the mu agonist action; mu receptors control the pain pathways in the medulla. Also, it has actions in the limbic and cortical systems that reduce the negative perception of pain.
(d) **Respiratory depression**: morphine can reduce the activity at the pontine respiratory center. It reduces the sensitivity to CO_2 and hypoxemia. It reduces the number of breaths per minute and can end in an apnea. This effect is dose dependent and directly relates with the mu agonism.

(e) **Antitussive**: it depresses the cough reflex at least in part by a direct effect on the cough center in the medulla. This mechanism is not well known and has no relation with analgesia or respiratory depression.
(f) **Miosis**: this effect is related with the disinhibition of the Edinger–Westphal nucleus at the oculomotor nerve. This effect does not show tolerance and could be adequate to detect recent use of opioids.
(g) **Nausea and vomit**: it is observed more frequently after the first administrations. It is caused by direct stimulation of the chemoreceptor trigger zone for emesis in the area postrema of the medulla.
(h) **Neuroendocrine actions**: morphine actions in the hypothalamus inhibit the release of gonadotropin-releasing hormone and corticotrophin-releasing hormone, producing a decrease in the luteinizing hormone, follicle-stimulating hormone, adrenocorticotropic hormone (ACTH), and beta-endorphin. It also stimulated the secretion of the antidiuretic hormone (ADH). By its effects in the hypothalamus, also a central hypothermia is observed.
(i) **Muscular tone**: myoclonus is a rare side effect, ranging from mild twitching to generalized spasm. In anesthetic use muscular rigidity can be observed.

The main peripheral actions are:

(a) **Gastrointestinal**: morphine can produce an increase in the tone of muscles of the gastrointestinal tract, including the sphincters, and a reduction in the motility. As a consequence, there is a reduction in the gastric emptying and in the peristaltism and a contraction of sphincter. Clinically it is related with constipation.
(b) **Cardiovascular**: it could produce hypotension by its action in the vasomotor center and by vasodilatation. Also a vagal bradycardia has been described. Also, there is a potential to increase intracranial pressure.
(c) **Histamine release**: in the face, neck, and upper thorax, there is a feeling of heat, flushing, and pruritus.
(d) **Renal**: morphine increases the tone of the detrusor muscle of bladder.

Pharmacokinetics

The pharmacokinetic properties of morphine and the rest of opioids described in this chapter are summarized in Table 28.2. The pharmacokinetics of morphine and its metabolites vary, depending on the route of administration. The oral bioavailability ranges from 35 % to 75 %, with a plasma half-life ranging from 2 to 3.5 h. The half-life is less than the time course of analgesia, which is 4–6 h, thus reducing the accumulation. Morphine as other opioids presents a significant first-pass metabolism in the liver with oral dosing. Morphine is biotransformed mainly by hepatic glucuronidation to the major but inactive metabolite morphine-3-glucuronide (M3G) and the biologically active morphine-6-glucuronide (M6G) compound in a lower percentage (10 %). The M6G has a longer elimination half-life than morphine (4 h vs. 2 h) and has a more powerful analgesic activity. This metabolite is related with both the pharmacological effect and the toxicity of morphine. Thus, the equivalence between parenteral and oral morphine varies depending on the frequency of the administration, being 1:6 after a single administration and 1:2 or 1:3 after multiple doses; this is due to the high concentrations of M6G that are reached after oral treatment.

Table 28.2 Pharmacokinetic properties of main opioids

Opioid	Oral bioavailability (%)	Half-life (h)	Plasma protein binding (%)	Duration of action (h)	10 mg morphine equivalence (analgesia)	
					im	po
Morphine	35–75	2–3	35	4–6	10	30–60
Diacetylmorphine	20–50	0.1	35	3–6	5	20
Methadone	70–80	15–40	80	24	10	20
Codeine	50	2–4	7	4	130	75
Buprenorphine	50(sl)/90(td)	3–5	96	6–8	0.3	0.8 (sl)
Oxycodone	60–87	3–4	45	12	–	6.7
Hydromorphone	30–40	5	8–19	3–5	1.5	7.5
Hydrocodone	NA	2–4	NA	NA	–	30
Meperidine	50	3	60	1.5–3	100	300
Pentazocine	10	2–3	60	3–6	60	150
LAAM	48	14–37	Poorly	48–72	–	24
Tramadol	68	6	4	4–6	100	100
Tapentadol	32	4–5	20	4–6	–	100–200
Naloxone	5–10	1–2	NA	0.5–2	–	–
Naltrexone	5–20	4–13[a]	20	24–72	–	–
Nalmefene	41	13	30	24	–	–

sl sublingual, *td* transdermal, *NA* non-available
[a]Half-life for 6-β-naltrexone

A study on MST pharmacodynamic and pharmacokinetic properties compared to methadone showed that it can be administered once a day and could be a good alternative in patients nonresponders to methadone (Mitchell et al. 2003), but there is still a lack of controlled studies in opioid-dependent patients (Jegu et al. 2011).

28.2.1.3 Diacetylmorphine (Diamorphine, Heroin)

Heroin was developed in the 1870s by Bayer Laboratories as a treatment for injected morphine dependence. It is synthesized from morphine by acetylation at the three and six positions and is twice more active than morphine at equivalent doses due to its higher lipophilic properties. It has analgesic and antitussive activities and also was used as a remedy in the late phases of tuberculosis.

There are several types of heroin in the market depending on its origin and characteristics:

(a) **Base heroin or Tsao-ta**: comes from Southeast Asia. Its color is white or dark and is used for injection or smoking.
(b) **The brown sugar**: is the heroin used to be smoked. It has been mixed with other substances as caffeine, strychnine, sugars, etc. Its heroin contents vary from 25 % to 50 %.
(c) **White heroin or hydrochloride**: is also known as the Thai heroin. Its use is predominantly intravenous. It has the higher active content, sometimes more than 90 %.

(d) **Black heroin or black tar heroin**: as its name indicates, its aspect is similar to tar; it is a black and sticky substance. It comes from America and its purity is around 20 %. It is used for injection.

Pharmacodynamics

Heroin acts as a mu agonist through its metabolites 6-monoacetylmorphine (6-MAM) and morphine. The effects of heroin are the same as other mu-opioid agonists. With heroin use, thyroid hormone levels may be elevated because of raised thyroid-binding globulin; thus, there are increased measures without abnormal function (Kreek 1978). Heroin, as other short-acting opioids, reduces rosettes formed by human T lymphocytes (Kreek 1978). The possible explanation could be the increase of cortisol levels during opioid withdrawal and the consequent suppression of immune function (Novick et al. 1989).

Pharmacokinetics

Heroin itself has no intrinsic opioid activity; but it is a very effective prodrug and metabolized in humans to active opioid compounds first by deacetylation to the active 6-monoacetylmorphine (6-MAM) and then by further deacetylation to morphine, when administered by parenteral route (Inturrisi et al. 1984). The bioavailability of diacetylmorphine, when measured by morphine concentrations, is 80 % by intranasal route, 89 % by the smoked route, and 45 % in the *chasing the dragon* type of use (Hendriks et al. 2001). Oral heroin has complete first-pass metabolism (Inturrisi et al. 1984) with an oral bioavailability of 20–50 % and has very limited systemic bioavailability (only 6-MAM and morphine can be found in the blood). Compared to morphine, heroin given intramuscularly is about two times as potent as morphine for pain relief with a faster onset of peak mood effect; however, it has less sustained effect (Cone et al. 1993).

Heroin has an average half-life in blood of 3 min after intravenous administration; the half-life of 6-monoacetylmorphine in humans appears to be 3–10 min (Inturrisi et al. 1984). The blood clearance of heroin is greater than the upper range of hepatic blood flow in humans, indicating that organs other than the liver are likely involved in the metabolism of heroin, such as the gastrointestinal wall and the kidney (Inturrisi et al. 1984), as well as hepatic carboxylesterases such as butyrylcholinesterase (Kamendulis et al. 1996).

The use of intranasal, intramuscular, and subcutaneous heroin all produces peak blood levels of heroin or 6-monoacetylmorphine within 5 min; however, intranasal use has about half the relative potency (Cone et al. 1993).

28.2.1.4 Methadone

Pharmacodynamics

Methadone is a semisynthetic opioid agonist that is used in the chronic treatment of pain and in the opioid dependence disorder. It was first synthesized by Bayer as an analgesic in Germany in the late 1930s and first studied for human use in the 1950s in the United States. It has been used as a maintenance treatment for heroin addiction since the first years of the 1960s (Dole et al. 1966).

Its mechanism of action is mediated by the activation of the opioid receptors, mainly the mu type. At higher doses it can effectively block the euphoric effects of exogenous opioids (Dole et al. 1966). Methadone is an agonist at mu-, delta-, and, to a lesser extent, kappa-opioid receptors (Kristensen et al. 1995). Methadone also displays *N*-methyl-D-aspartate (NMDA) receptor antagonist properties, which affect the development of tolerance (Davis and Inturrisi 1999).

Methadone and its main metabolites, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) and 2-ethyl-5-methyl-3,3-diphenyl-1-pyrrolidine (EMDP), are chiral molecules, which means that methadone has an asymmetrical carbon atom in its structure, implying that it exists in two enantiomeric forms, having the same chemical structure but different spatial arrangements, with one enantiomer being the mirror image of the other. Methadone is usually administered as a racemate, a 50:50 mixture of two enantiomers called (*R*)- or levo- or L-methadone and (*S*)- or dextro- or D-methadone. (*R*)-methadone has a higher affinity for opioid receptors and an increased analgesic potency than the (*S*)-enantiomer (Eap et al. 2002). Despite lacking strong opioid effects, (*S*)-methadone may be a clinically important determinant of (*R, S*)-methadone's therapeutic and adverse responses (negative mood effects – tension, fatigue, confusion, etc.) (Mitchell et al. 2004). Although (*R*)-methadone is believed to account for most, if not all, of the therapeutic effects of methadone maintenance treatment, (*R, S*)-methadone is normally used in therapeutics due to its lower production costs and an evidence that it produces similar therapeutic outcomes when compared with (*R*)-methadone alone (Eap et al. 1996; de Vos et al. 1998).

The adverse events of methadone are similar to those of morphine. In general, they are mild and not severe; the most common are constipation, sweating, and insomnia which tend to lessen due to the development of tolerance (Kreek et al. 1983; Kreek 1973). There is also a central effect, consisting in the persistence of the pulsatile increase in prolactin related to the peak level of methadone, which occurs approximately 2–4 h after daily administration (Kreek 1978).

There are two important adverse events related to methadone: the risk of respiratory depression and the risk of cardiac rhythm disorders related to QT interval prolongation (Eap et al. 2002; Chugh et al. 2008). A QT interval longer than 500 ms increases the risk of polymorphic ventricular tachycardia, such as torsade de pointes (TdP) (Schwartz et al. 1993). Other authors have also described QT prolongation and/or TdP appearance in MMT (Andrews et al. 2009; Krantz et al. 2009). The mechanism of this increase has been related to the inhibitory action of methadone on the hERG voltage-gated potassium channel and also could be related to the blockade of calcium channels in the cardiac myocyte membrane and the induction of bradycardia. Usually, patients with QTc prolongation present other risk factors and are exposed to higher doses of methadone (Fonseca et al. 2009).

Chronic administration of methadone (as with other long-acting opioids) leads to the gradual development of tolerance to the effects on hypothalamic-releasing factors, with resumption of normal menses and return of plasma levels of testosterone to normal within 1 year as well as return to normal levels and activity of

anterior pituitary-derived ACTH and beta-endorphin and normal ACTH stimulation in approximately 3 months. Prolactin levels still rise after oral methadone dosing; however, both peak plasma levels of methadone and also prolactin are found at 2–4 h after dosing; prolactin levels usually do not exceed the upper limit of normal (Kreek 1973).

Pharmacokinetics

Methadone is rapidly absorbed after an oral dose, it can be detected in the blood at 15–45 min after oral administration, and peak plasma concentrations occur at 2–4 h after dosing (Eap et al. 2002). The oral bioavailability of methadone was found to be around 70–80 % in a range of doses of 10–60 mg with large intersubject variations. Methadone is highly bound to plasma proteins, including albumin, lipoproteins, and mainly to alpha-1-glycoprotein. Enantiomeric differences are also relevant in protein binding (the unbound fraction for (*S*)-methadone is 10 % while for the (*R*)-enantiomer is 14 %) and its metabolic disposition. Although administered as a racemic mixture that contains the same amounts of (*R*)-methadone and (*S*)-methadone, the (*R*)-/(*S*)-methadone ratio varies significantly over the 24-h administration interval in steady-state conditions; and also, large interindividual differences can be seen in the (*R*)-/(*S*)-methadone ratio (Eap et al. 1996). All these variables might contribute to interindividual response differences to methadone treatment. Methadone is extensively metabolized in the body, mainly by CYP3A4 in liver, and in the intestinal epithelium, and to a lesser extent by CYP2B6 and CYP2D6. Its main metabolite (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP)) is inactive: it is formed by *N*-demethylation and spontaneous cyclization methadone half-life is about 28 h with a large interindividual variability (between 4 and 91 h). (*R*)-methadone has a longer half-life than (*S*)-methadone (38 vs. 29 h, respectively). After chronic administration, a reduction in half-life (from 55 to 22 h) has been detected because it induces its own metabolism regulated by cytochrome P450 CYP3A4 (Wolff et al. 2000).

The elimination of methadone is mostly due to metabolic clearance. The limited amounts of circulating drug that undergo glomerular filtration are partially reabsorbed by the kidney tubules, and this reabsorption is pH dependent. Methadone clearance varies from 23 to 210 ml/min, and there are significant differences between both enantiomers (158 ml/min vs. 129 ml/min for (*R*)- and (*S*)-methadone, respectively). Urinary pH has profound effects on methadone excretion and on the volume of distribution of the drug. By keeping the urinary pH constant, the interindividual differences of methadone elimination and plasma concentrations are considerably reduced.

28.2.1.5 Codeine

Codeine is one of several naturally occurring alkaloids found in opium. It is methylmorphine, with methyl substitution on the phenolic hydroxyl group of morphine. It is more lipophilic than morphine and thus crosses the blood–brain barrier faster. Its oral bioavailability is greater than that of morphine.

Pharmacodynamics

Codeine has very low affinity for opioid receptors; it is active because it is metabolized in part to morphine. Codeine is commonly used to suppress cough at doses lower than used for analgesia (starting with 10–20 mg given orally), which can be increased to higher doses for chronic (lower airway) cough. Codeine reduces cough via a central mechanism, with doses greater than 65 mg not indicated owing to little increased effect with increasing side effects (Yaksh and Wallace 2011).

Pharmacokinetics

Codeine undergoes *O*-dealkylation to morphine. The conversion is catalyzed by CYP2D6 (the same enzyme also converts dihydrocodeine, hydrocodone, and oxycodone). Other metabolites are mostly inactive and excreted in the urine; about 10 % are demethylated to morphine via CYP2D6, which are mostly responsible for the analgesic effect of codeine. Genetic variations in this enzyme system, complete or partial lacking of CYP2D6 (poor metabolizers), may result in lower or no production of morphine, and the subjects carrying this polymorphism would experience less effects of codeine, but those with multiple duplications of CYP2D6 (ultra metabolizer, ultrafast metabolizer) can transform abnormally large amounts of codeine into morphine and have the risk of intoxication. Repeated doses of codeine may result in the accumulation of the active metabolite M6G in patients with renal disease.

28.2.1.6 Buprenorphine

Buprenorphine is a semisynthetic opioid that, like oxycodone, is derived from thebaine. The chemical structure of buprenorphine is that of an oripavine with a C7 side chain, which contains a tert-butyl group. It is primarily mu-opioid receptor partial agonist and a kappa antagonist with a ceiling effect. Buprenorphine alone and in combination with naloxone was approved in 2002 by the FDA as an office-based sublingual treatment for heroin and opioid addiction (Borg et al. 2009). Norbuprenorphine is a major metabolite of buprenorphine in humans, with activity at the mu-opioid receptor (Huang et al. 2001).

Pharmacodynamics

Initially developed as an analgesic, buprenorphine has been shown in most studies to be as effective as morphine in many situations. It is 25–50 times more potent than morphine. Buprenorphine has some modest kappa-opioid receptor activity, and it has been shown that the kappa activity of buprenorphine is that of an antagonist (Cowan 2007). Also, an agonistic effect on the opioid receptor-like (ORL1) receptor has been described that has been also related to its characteristic ceiling effect (Lutfy and Cowan 2004). Buprenorphine has high affinity for, but low intrinsic activity at, mu receptors and displaces some full opioid agonists from receptors (Strain et al. 2002). For this reason, and because of buprenorphine's higher affinity for the mu receptor, full agonists cannot displace it and therefore will not exert a dose-related opioid effect on the receptors already occupied by buprenorphine, and also it can induce a withdrawal syndrome in subjects using full opioid agonists (Comer et al. 2001; Strain et al. 1995).

Owing to its ceiling effect, increasing doses in humans beyond 32 mg sublingually has no greater opioid agonist effect. Two important properties of buprenorphine are relevant: its apparent lower severity of withdrawal signs and symptoms on cessation, compared with heroin and methadone (San et al. 1992), and its reduced potential to produce lethal overdose when used alone in opiate-naive or nontolerant persons because of its partial agonist properties. However, it is not clear whether there is a ceiling for this effect; the respiratory depression and other effects of buprenorphine can be prevented by prior administration of naloxone, but they are not readily reversed by high doses of naloxone once the effects have been produced (Megarbane et al. 2010). This suggests that buprenorphine dissociates very slowly from opioid receptors.

As a partial mu agonist, it may cause symptoms of abstinence in patients who have been receiving receptor agonists for several weeks.

Pharmacokinetics

Buprenorphine has poor gastrointestinal bioavailability and fair sublingual bioavailability (Brewster et al. 1981). FDA-approved formulations of the drug for the treatment of opioid addiction are in the form of sublingual tablets that are held under the tongue and absorbed through the sublingual mucosa; also, a sublingual buprenorphine–naloxone film has been recently approved in some countries (Lintzeris et al. 2013). Concentrations in blood peak within 5 min of intramuscular injection and within 1–2 h of oral or sublingual administration. About 96 % of the circulating drug is bound to protein. Both *N*-dealkylated and conjugated metabolites are detected in the urine, but most of the drug is excreted unchanged in the feces.

Like morphine, the major metabolic pathway for buprenorphine is glucuronidation, not the oxidation. Buprenorphine is metabolized to norbuprenorphine, which occurs by dealkylation in the cytochrome P450-related enzyme 3A4 system, of which buprenorphine itself is a weak inhibitor (Yaksh and Wallace 2011). Buprenorphine undergoes extensive first pass in the liver; thus, it is administered sublingually with 50–60 % bioavailability.

A high percentage of buprenorphine is bound to plasma protein. The 3A4 metabolism involves some possible interactions with other drugs as antiretrovirals being less than with methadone; however, buprenorphine has not been so extensively studied (McCance-Katz and Mandell 2010).

The terminal elimination half-life of buprenorphine is long, and there is considerable variation in reported values (mean values ranging from 3 to 44 h). Most of a dose of buprenorphine is eliminated in the feces, with approximately 10–30 % excreted in urine (Elkader and Sproule 2005). Buprenorphine has a long duration of action (24–48 h) when administered on a chronic basis, not because of its pharmacokinetic profile but because of its very slow dissociation from mu-opioid receptors.

Despite the ceiling effect of buprenorphine as previously described, there have been a number of reported cases of deaths in Europe with concurrent benzodiazepine abuse (Lintzeris et al. 2007). After the report in many countries of the buprenorphine diversion and the intravenous misuse, a new formulation was developed in combination with naloxone (Yokell et al. 2011). In this formulation,

naloxone will not precipitate withdrawal when taken sublingually because of its limited oral bioavailability; however, it may block the initial euphoric effects of buprenorphine if abused by the intravenous route and may also then precipitate acute opioid withdrawal (Mendelson and Jones 2003). The 4:1 ratio of buprenorphine to naloxone reduces any pleasurable effects of intravenous buprenorphine by blocking a small percentage of opioid receptors and may also produce modest withdrawal symptoms (Mendelson and Jones 2003). However, this effect is reduced in the presence of benzodiazepines.

28.2.1.7 Oxycodone

Oxycodone is a semisynthetic compound derived from thebaine, with agonist activity, primarily at mu receptors. Oxycodone has been used clinically since the early 1900s. It is combined with aspirin or acetaminophen for moderate pain and is available orally without coanalgesic for severe pain. It is a popular drug of abuse, especially in the controlled-release formulation, which can be crushed for a potentially toxic, rapid "high" comparable to the effects of the immediate-release formulation (Webster et al. 2012).

Pharmacokinetics

The onset of action begins after 1 h, and in controlled-release form, it lasts for approximately 12 h, with a plasma half-life of 3–4 h for the immediate release. Stable plasma levels are achieved within 24 h. Oral bioavailability ranges from 60 % to 87 %, with 45 % protein bound. Oxycodone is mostly metabolized in the liver, with the remainder as well as the metabolites metabolized in the kidneys. It is *O*-demethylated (CYP2D6) to oxymorphone and *N*-demethylated (CYP3A4 and CYP3A5 mediated) to noroxycodone (more abundant) (Lugo and Kern 2004). Oxymorphone is also a potent analgesic, and noroxycodone is a weaker analgesic (Lugo and Kern 2004).

In terms of protein binding and lipophilicity, oxycodone is similar to morphine, with slightly longer half-life and greater bioavailability. Unlike morphine, oxycodone is metabolized mostly by the cytochrome enzyme CYP2D6.

28.2.1.8 Hydromorphone

Hydromorphone is a semisynthetic opioid agonist and a hydrogenated ketone of morphine. It was first synthesized in Germany in 1921 and was introduced into clinical practice by 1926 (Murray and Hagen 2005). Hydromorphone has commonly been viewed as a second-line drug in the treatment of pain, although being more potent than morphine (five times more potent when given orally and 8.5 times as potent when given intravenously) (Murray and Hagen 2005). It is used for the treatment of acute pain, chronic cancer pain, and, to a lesser extent, chronic nonmalignant pain (Murray and Hagen 2005). It is excreted along with its metabolites by the kidney. It can be given intravenously, by infusion, orally, and per rectum, with low oral bioavailability.

Recently, an osmotic controlled-release oral delivery system (OROS) hydromorphone extended release has been designed, which allows once-daily dosing. Some clinical trials have been performed to evaluate the convertibility of other opioids in chronic pain. The side effects are comparable to other opioids.

Pharmacokinetics

Hydromorphone is shorter acting than morphine. It is derived from morphine, although it may also be produced in the body in small amounts by *N*-demethylation of hydrocodone. It has an oral bioavailability of 30–40 %, with an analgesic onset after 10–20 min, which peaks at about 30–60 min and persists for about 3–5 h. The oral–parenteral ratio is about 5:1, with an equivalency of 1.5 mg of hydrocodone to 10 mg morphine (Murray and Hagen 2005).

28.2.1.9 Hydrocodone

Hydrocodone is a prescription drug frequently used for relatively minor (such as dental) pain. It is often used in combination with acetaminophen; thus, there can be hepatotoxicity associated with its abuse. Hydrocodone has the same potency as morphine on a milligram-for-milligram basis.

Pharmacokinetics

Hydrocodone is well absorbed from the gastrointestinal tract. The peak plasma concentration appears after 1.3 h of its administration and has a half-life of 2–4 h, with a peak effect at 0.5–1 h (McEvoy 2007). Its duration of action is 3–4 h. It is metabolized by CYP3A4 and CYP2D6, and its main metabolites are norhydrocodone and hydromorphone. Codeine may show up as trace quantities of hydrocodone in urine testing as up to 11 % of codeine is metabolized to hydrocodone (Oyler et al. 2000), which could be misinterpreted as hydrocodone abuse.

28.2.1.10 Meperidine

Meperidine or pethidine is a phenylpiperidine. It was first developed as an anticholinergic agent. It is mostly effective in the CNS and bowel; however, it is no longer used for treatment of chronic pain owing to concerns regarding toxicity of its metabolite and should not be used for more than 48 h or at doses above 600 mg/day. It has serotonergic activity when combined with monoamine oxidase inhibitors (MAOIs), which can produce serotonin toxicity (clonus, hyperreflexia, hyperthermia, and agitation); besides, the analgesic effects of meperidine are not pronounced (Latta et al. 2002).

Pharmacodynamics

Meperidine is a potent mu agonist yielding strong analgesic actions. Peak respiratory depression is observed within 1 h of intramuscular administration, and there is a return toward normal starting at 2 h, approximately. Like other opioids, meperidine causes pupillary constriction, increases the sensitivity of the labyrinthine apparatus, and has effects on the secretion of pituitary hormones similar to those of morphine. Meperidine sometimes causes CNS excitation, characterized by tremors, muscle twitches, and seizures; these effects are due largely to the accumulation of a metabolite, normeperidine. Meperidine has well-known local anesthetic properties, particularly noted after epidural administration. As with morphine, respiratory depression is responsible for an accumulation of CO_2.

Meperidine can release histamine following parenteral administration. Due to its effects on the smooth muscle, meperidine can slow gastric emptying; however, it does not cause as much constipation as morphine.

Pharmacokinetics

Meperidine is absorbed by all routes of administration, but the rate of absorption may be erratic after intramuscular injection. By the oral route, the onset of analgesia begins after 15 min, with peak in 1–2 h, which is close to the peak level in plasma, with duration of about 1.5–3 h (Yaksh and Wallace 2011). It is absorbed by all routes, but intramuscular administration results in a less reliable peak plasma level after 45 min, with a wide range of plasma concentrations. After oral administration, about 50 % of the drug enters the circulation without first-pass metabolism, with peak at 1–2 h. Sixty percent of meperidine is protein bound, and little is excreted unmetabolized (Latta et al. 2002). Meperidine is mostly metabolized in the liver, with half-life of about 3 h. In humans, meperidine is hydrolyzed to meperidinic acid, which in turn is partially conjugated. Meperidine also is *N*-demethylated to normeperidine, which then may be hydrolyzed to normeperidinic acid and subsequently conjugated. Normeperidine has modest analgesic properties, but it is a potent CNS stimulant and can cause seizures (Yaksh and Wallace 2011).

28.2.1.11 Pentazocine

Pentazocine was approved in the late 1960s, both the oral and the parental formulations. It is a partial agonist or antagonist at mu receptor and also a kappa receptor partial agonist. For analgesia, it has been manufactured also with acetaminophen. Later, it was manufactured in combination with naloxone to diminish its intravenous use. Its abuse declined after this change in the formulation according to DAWN emergency room register (Fudala and Johnson 2006).

Pharmacodynamics

The pattern of CNS effects produced by pentazocine generally is similar to that of the morphine-like opioids, including analgesia, sedation, and respiratory depression. The analgesic effects of pentazocine are due to agonistic actions at opioid receptors but present a ceiling effect. The cardiovascular responses to pentazocine differ from those seen with typical receptor agonists, in that high doses cause an increase in blood pressure and heart rate. Pentazocine does not antagonize the respiratory depression produced by morphine. However, when given to patients dependent on morphine or other *mu* agonists, pentazocine may precipitate withdrawal due to its partial agonist–antagonist actions at the *mu* receptor. At high doses (60–90 mg), pentazocine elicits dysphoric and psychotomimetic effects, probably due to its kappa agonist properties.

Pharmacokinetics

Pentazocine is a mixed agonist–antagonist that can be given intramuscularly or orally but is not currently available in the oral formulation. Because it can cause psychotomimetic effects, it has a very limited role in the treatment of chronic pain.

Its duration of action is 3–6 h. Its peak effect is at 0.5–1 h when given intramuscularly and 1–2 h when given orally. Sixty percent of the drug is bound to protein. Pentazocine is metabolized by the liver via oxidative and glucuronide conjugation with an extensive first-pass effect. When administered orally, the bioavailability of pentazocine is about 10 %, except in patients with cirrhosis, which increases bioavailability to 60–70 %. The drug half-life is 2–3 h. Small amounts of unchanged pentazocine are excreted with urine (Yaksh and Wallace 2011).

28.2.1.12 LAAM

Levacetylmethadol or levomethadyl acetate or levo-α-acetylmethadol (LAAM) is a synthetic, longer-acting (48-h) congener of methadone that also is orally effective. LAAM was first studied in the 1970s for the treatment of heroin addiction and approved in 1993 by the FDA after a large multicenter safety trial (Kreek and Vocci 2002). Postmarketing, after reports of prolonged QTc intervals on electrocardiogram leading to torsade de pointes that may have been caused by LAAM, a black-box warning was added to the product label and marketing continued in the United States until 2003. LAAM was withdrawn from the European countries at 2001. This effect may have been the result of preexisting cardiac disease or undefined drug interactions (Kreek and Vocci 2002). At this moment, LAAM is not marketed by any pharmaceutical company.

LAAM acts as a pure opioid agonist, active mostly at the mu-opioid receptor (Yaksh and Wallace 2011; Kreek and Vocci 2002).

Pharmacokinetics

LAAM shares with methadone the properties of long duration of effect (48 h vs. 24 h for methadone), in part owing to its active metabolites nor-LAAM and dinor-LAAM, as well as its steady-state perfusion of mu-opioid receptors. LAAM was previously considered a prodrug, but this was refused in a study (Walsh et al. 1998) showing that intravenous LAAM produced significant subjective and physiological effects that appeared within 5 min, whereas the effects of oral LAAM appeared more slowly within 1–2 h after drug administration; the pharmacokinetic data indicate that the immediate effects of intravenous LAAM could be attributable to the parent drug rather than the active metabolites.

Oral LAAM undergoes extensive first-pass metabolism to the active demethylated metabolite nor-LAAM, which is further demethylated to a second active metabolite, dinor-LAAM. These metabolites are more potent than the parent drug. Oral bioavailability is less than 50 %. Nor-LAAM and dinor-LAAM accumulate with chronic administration. In addition, LAAM and its metabolites bind to tissue proteins. The clearance of nor-LAAM and LAAM is similar, whereas the clearance of dinor-LAAM is more prolonged than that of its parent compound. The peak pharmacological effect of LAAM as measured by the amount of pupillary constriction occurred at 8 h and then diminished at a rate most like that of nor-LAAM metabolism (Borg et al. 2009).

LAAM is metabolized in the gut wall and liver to active metabolites, nor-LAAM and dinor-LAAM, through sequential demethylation (Walsh et al. 1998).

Because of the metabolism of LAAM by the cytochrome P450 3A4 system-related microsomal enzymes to nor-LAAM and dinor-LAAM, drug interactions can occur (e.g., rifampin and long-term alcohol abuse tend to induce this enzyme system). In their presence, increased biotransformation of LAAM could accelerate the production of nor-LAAM and dinor-LAAM. LAAM metabolism theoretically could be retarded if hepatic drug metabolism is diminished, as occurs either in the presence of very large quantities of ethanol or perhaps with large doses of benzodiazepines or with intake of cimetidine (Borg et al. 2009).

28.2.1.13 Tramadol

Tramadol is a synthetic codeine and morphine analog that is a weak mu agonist. It also exerts some capacity to inhibit the uptake of norepinephrine and serotonin. It is more effective in the treatment of the mild and moderate pain than in the treatment of severe and chronic pain (Yaksh and Wallace 2011). Misuse, diversion, physical dependence, abuse, addiction, and withdrawal have been reported in conjunction with the use of tramadol. Tramadol has been shown to reinitiate physical dependence in some patients who have previously been dependent on other opioids; thus, it should be avoided in patients with a history of addiction (Mayor 2013).

Pharmacodynamics

Tramadol is a chiral molecule, administered as a racemic mixture; the (R)-enantiomer and the metabolite (*R*)-*O*-desmethyltramadol (M1) are agonists of the μ-opioid receptor, and they inhibit serotonin reuptake. The (*S*)-enantiomer inhibits norepinephrine reuptake and stimulates two adrenergic receptors (Lewis and Han 1997). As a consequence, the (S) form enhances the inhibitory effects on pain transmission in the spinal cord.

The pharmacological effects are similar to those of morphine, and the main adverse effects include nausea, vomiting, dizziness, dry mouth, sedation, and headache. Respiratory depression and constipation are mild compared to morphine. Tramadol can cause seizures and possibly exacerbate seizures in patients with predisposing factors. Some effects of tramadol can be reversed by naloxone as respiratory depression, but not the analgesia. There is an increased risk of seizures with the combined use of tramadol and naloxone.

Pharmacokinetics

Tramadol has a bioavailability of 100 % after an intramuscular dose and 68 % after an oral dose. Its affinity for the mu-opioid receptor is weaker than morphine, but the *O*-demethylated metabolite M1 is two to four times as potent as the parent drug and may account for part of the analgesic effect.

Tramadol is metabolized in the liver, mainly by CYP2D6 and CYP3A4, thus explaining some reported cases of interactions with methadone (Leavitt 2005), and also undergoes conjugation and renal excretion. Poor metabolizers of CYP2D6 have less analgesic effects due to lower levels of *O*-desmethyltramadol (M1). The elimination half-life is 6 h for tramadol and 7.5 h for its active metabolite. Analgesia begins within an hour of oral dosing and peaks within 2–3 h. The duration

of analgesia is approximately 6 h. The maximum recommended daily dose is 400 mg (Yaksh and Wallace 2011).

28.2.1.14 Tapentadol

Tapentadol is a centrally acting synthetic analgesic, indicated for the management of moderate to severe acute pain in adults. The recommended doses are 50 mg, 75 mg, or 100 mg every 4–6 h depending upon pain intensity. Daily doses greater 600 mg are not recommended. In the case of the extended-release preparation, usual doses are 100–250 mg twice daily. Tapentadol immediate release was originally approved by the FDA in November 2008, and in 2011, the extended-release formulation (Hartrick and Rozek 2011; Hoy 2012).

Pharmacodynamics

Tapentadol exact mechanism of action is unknown. Preclinical studies have shown that tapentadol is a mu-opioid receptor agonist and a norepinephrine reuptake inhibitor. It is 18 times less potent than morphine in binding to the human mu-opioid receptor and is two to three times less potent in producing analgesia in animal models. Tapentadol has been shown to inhibit norepinephrine reuptake resulting in increased norepinephrine concentrations. The principal therapeutic action of tapentadol is analgesia. As other opioids, tapentadol causes respiratory depression, tolerance, and dependence (Hartrick and Rozek 2011; Hoy 2012).

Pharmacokinetics

Absolute bioavailability is approximately 32 % due to extensive first-pass metabolism. Maximum serum concentrations of tapentadol are observed at around 1.25 h after dosing. In extended-release formulations, maximum serum concentrations are observed between 3 and 6 h after administration.

The major pathway of tapentadol metabolism is conjugation with glucuronic acid. After oral administration approximately 70 % of the dose is excreted in the urine in the conjugated form (55 % *O*-glucuronide and 15 % sulfate of tapentadol). Only 3 % of drug was excreted in the urine as unchanged drug. In addition, tapentadol is metabolized to *N*-desmethyl tapentadol (13 %) by CYP2C9 and CYP2C19 and to hydroxyl tapentadol (2 %) by CYP2D6, which are further metabolized by conjugation. None of the metabolites contribute to the analgesic activity. Tapentadol and its metabolites are excreted almost exclusively (99 %) via the kidneys. The terminal half-life is on average 4–5 h after oral administration (Hartrick and Rozek 2011; Hoy 2012).

28.2.1.15 Naloxone

Naloxone is a pure opioid antagonist for parenteral use. It is an *N*-allyl derivative of oxymorphone. Naloxone is competitive antagonist at all opioid receptors, but it has greatest affinity for mu receptors. Naloxone is usually administered in the emergency department to revert heroin overdoses and also as an aid to distinguish causes of coma (if patient does not respond to naloxone, nonopioid causes should be considered) (Boyer 2012).

Pharmacodynamics

Small doses of naloxone reliably reverse or prevent the effects of pure opioid agonists and most mixed agonists–antagonists (Schäfer 2011; Mitchell et al. 2003). However, given alone, naloxone is nearly devoid of clinically demonstrable effects. In humans, extremely large doses (4 mg/kg) cause a mild increase in heart rate and systolic blood pressure, as well as slowing of EEG alpha-wave activity.

Pharmacokinetics

Naloxone is widely distributed and rapidly achieves effective concentrations in the CNS after parenteral administration. Plasma and brain concentrations fall precipitously because of rapid redistribution. The drug is rapidly cleared by hepatic biotransformation, mainly to the 3-glucuronide. The clearance is very high (approximately 30 ml kg^{-1} min^{-1}), which suggests that extrahepatic elimination may be occurring. The terminal half-life is 1–2 h. The onset of antagonist effect is extremely rapid, but the duration of action is quite brief. The duration of naloxone is nearly always shorter than that of the opioids whose effects it is intended to antagonize. It has to be taken into account that opioid reversal can sometimes have important hemodynamic consequences. Increases in systemic pressure, heart rate, and plasma levels of catecholamines can occur. Oral or sublingual administration of naloxone has very low systemic bioavailability due to marked hepatic first-pass metabolism. Enteral naloxone can block opioid action at the intestinal receptor level but has no general effects.

28.2.1.16 Naltrexone

Naltrexone is an opioid antagonist, chemically related to naloxone. Compared to naloxone, it has higher oral bioavailability and a longer duration of action. Naltrexone has been used for relapse prevention in opioid dependence because of its ability to antagonize all the actions of opioids. Also, there is evidence that naltrexone blocks activation by alcohol of dopaminergic pathways in the brain that are thought to be critical to reward, so it is used also in the treatment of alcohol dependence, as relapse prevention substance.

A depot formulation of naltrexone that provides 30 days of medication after a single injection has been approved for the treatment of alcoholism and heroin dependence in detoxified patients (Lobmaier et al. 2011). This formulation eliminates the necessity of daily pill-taking and prevent relapse when the recently detoxified patient leaves a protected environment (Krupitsky et al. 2011).

Pharmacodynamics

If administered at doses of 25 mg/day, it blocks completely the *mu*-opioid receptor, impeding the effects of the opioid agonists. If administered in alcohol-dependent subjects (doses of 50 mg/day), patients experience less craving for alcohol and less feelings of reward if they drink alcohol. A pharmacogenomic-related response to naltrexone in opioid-dependent subjects at mu receptor gene (OPRM1) has been described: those patients carrying the Asp40 allele had an increased percentage of days abstinent and a decreased percentage of heavy drinking days if treated with

naltrexone versus placebo, while those with the Asn40/Asn40 genotype showed no medication differences (Anton et al. 2008).

The most common side effect of naltrexone is nausea. An increase of transaminases could be observed, and if the dose is excessive, it can cause liver damage (Rosow and Dershwitz 2011).

Pharmacokinetics

Naltrexone is rapidly absorbed and undergoes 95 % first-pass metabolism to 6-β-naltrexol. This is an active metabolite that probably accounts for most of the naltrexone activity. The metabolite accumulates during chronic treatment and has a terminal half-life of 12.9 h, so significant antagonist effects may persist for 2–3 days after naltrexone is stopped.

28.2.1.17 Nalmefene

Nalmefene is another long-lasting opioid antagonist. It is the 6-methylene derivative of naltrexone. It is an antagonist at the mu- and delta-opioid receptors and a partial agonist at the kappa receptors (Soyka and Rosner 2010); there is no evidence of activity in any other receptor. Some advantages over naltrexone have been described, including greater oral bioavailability (Gal et al. 1986), longer duration of action (Gal et al. 1986; Ingman et al. 2005), and lack of dose-dependent liver toxicity (Mason et al. 1999).

As said previously, nalmefene also exerts a kappa partial agonism; the kappa-opioid system has been associated with motivational aspects in alcohol dependence, and nalmefene has been associated with a decreased alcohol self-administration in preclinical studies (Walker and Koob 2008).

Pharmacokinetics

Nalmefene is rapidly absorbed; the mean half-life was 13.4 h after single and repeated dosing, meaning that it has linear pharmacokinetics (Soyka and Rosner 2010). A slow dissociation of the drug from the mu-opioid receptor has been described. A clearance half-life of 28.7 ± 5.9 h has been reported for central opioid receptors and a plasma elimination half-life of 8.30 ± 0.34 h. Oral nalmefene may block receptors for longer and have a longer half-life over 24 h than naltrexone (Soyka and Rosner 2010). There is no evidence of any serious adverse drug reactions in hepatic or other body systems.

28.2.2 Treatment of Opioid-Related Disorders

Opioid addiction is a chronic and relapsing disorder with high costs to individuals, families, and society. Opiates, including the increasing abuse of prescription opioids, continue to be the main problem drug worldwide. The total number of opiate users at the global level is now estimated around 16.5 million people or 0.4 % of the population aged 15–64. A high prevalence for opiate use has been reported from Southwest and Central Asia, Eastern and

Table 28.3 Main strategies in opioid-related disorder treatment

	Type	Objective	Process	Pharmacological treatment
Opioid acute intoxication	Opioid overdoses	Decrease mortality	Revert opioid intoxication	Naloxone
Opioid withdrawal	Opioid detoxification	Avoid withdrawal syndrome	Detoxification	Methadone Buprenorphine Clonidine/lofexidine
Opioid addiction	Total abstinence oriented	Remove the opioid	Detoxification + Continued total abstinence	Methadone Buprenorphine Clonidine/lofexidine +/− Naltrexone
	Opioid agonist maintenance	Stabilization Harm reduction	Stabilizes brain neurochemistry Functional improvement	Agonist maintenance treatment Needle exchange and other risk reduction strategies

Southeastern Europe, and North America (United Nations Office on Drugs and Crime 2013).

The text revision of the fifth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5) divides opioid-related disorders into opioid addiction, opioid intoxication, opioid withdrawal, and other opioid-induced disorders (i.e., induced depression, induced anxiety, etc.)

Opioid addiction includes physiological, behavioral, and cognitive symptoms, ending in a repeated use of opioid drugs, despite significant problems related to such use, and is characterized by compulsion to seek and take the drug; as in other drug dependence, there is a loss of control in limiting the intake and emergence of a negative emotional state (i.e., dysphoria, anxiety, irritability) reflecting a motivational withdrawal syndrome when access to the drug is prevented (Koob and Volkow 2010). Opioid addiction can be mild, moderate, or severe depending on the number of criteria fulfilled.

In this section we present the main therapeutic strategies used in the treatment of opiate overdose, withdrawal, and addiction (Table 28.3).

28.2.2.1 Opiate Overdose

Opiate overdose is a life-threatening emergency. Typical signs are depressed consciousness, depressed respirations, and miotic pupils. The treatment goal is to sustain or restore vital functions and to immediately reverse the overdose with an opioid antagonist (naloxone).

First, it is essential to maintain the air pathway, and then, to avoid aspiration, put the patient in lateral decubitus position; if necessary, in case of cardiopulmonary arrest, mechanical ventilation should be applied.

The administration of naloxone 0.2–0.4 mg intravenously will begin to reverse the effects of an opiate overdose within 1 min. If there is no response to the initial dose, repeat doses may be administered every 2–3 min (0.5 mg, 2 mg, 4 mg, and 10 mg).

If the patient has no response to 10 mg, then an opioid likely is not responsible for the respiratory depression.

Finally, once the consciousness level is reverted, it is important to investigate a possible suicide intention risk of the patient and to perform a psychiatric assessment.

28.2.2.2 Opiate Withdrawal Syndromes

The withdrawal syndrome for short-acting opiates (heroin or morphine) begins 6–12 h after last use. Early symptoms include opiate craving, anorexia, anxiety, and irritability. These are coupled with clinical signs of increased respirations and blood pressure, sweating and yawning, rhinorrhea, lacrimation, piloerection (gooseflesh), tremor, and dilated pupils. After 48–72 h, the symptoms progress to include nausea, vomiting, diarrhea, insomnia, tachycardia, abdominal cramps, and involuntary muscle spasms and limb movements. Signs subside over 5–7 days. Signs and symptoms associated with withdrawal from long-acting opioids such as methadone are similar to those described above, but they may not begin until 24–48 h after the last dose and may last for 2–3 weeks or more. Withdrawal syndrome of buprenorphine is similar to other long-acting opioids, but it is usually less intense and of shorter duration. Withdrawal can also appear when an opioid antagonist, such as naloxone or naltrexone, is provided to a subject under any opioid agonist drug use; this is called precipitated withdrawal.

28.2.2.3 Treatment of Opioid Addiction

Opioid dependence is a complex and relapsing disorder with high rates of comorbidity (psychiatric disorders, infections such as HIV and hepatitis C), mortality (overdose), and legal and social problems (Sellman 2010). The two main therapeutic strategies in opioid dependence are as follows: abstinence-oriented treatments and maintenance treatments (Veilleux et al. 2010).

28.2.2.4 Total Abstinence-Oriented Treatments

In the abstinence-oriented treatments, the goal is to remove the opioid in a controlled fashion, with a complete eradication of the opioid agonist treatment. Abstinence is usually achieved in two stages: detoxification and relapse prevention.

Detoxification

Detoxification involves the substitution of the abused opioid by other long half-life opioid agonist or partial agonist (methadone or buprenorphine, usually) or an alpha2-adrenergic agonist (clonidine or lofexidine) and a progressive reduction in order to reduce the intensity of the withdrawal syndrome (Amato et al. 2005a; Gowing et al. 2009a, b).

When comparing detoxification treatments, methadone versus alpha2-adrenergic agonist treatments, studies showed similar results by means of withdrawal intensity and treatment completion (Gowing et al. 2009b). However, participants stayed in treatment for longer and experienced fewer adverse side effects on methadone and buprenorphine (Ziedonis et al. 2009). Also, clonidine, the most frequently tested

alpha2-adrenergic agonist, has been associated with potentially hazardous side effects as sedation and hypotension (Gowing et al. 2009b).

Methadone detoxification guidelines recommend to start with an initial dose of 10–45 mg/day, orally, depending on the severity of opioid withdrawal symptoms. Every 2 h it is necessary to assess the intensity of withdrawal and ensure that the dose will not exceed 60 mg/day. The same dose of the first day should be administered for 2–3 days and then reduced to 5–10 mg/day until total suppression. The detoxification usually lasts 10–20 days.

When buprenorphine (or buprenorphine–naloxone) is used in the detoxification treatment, initial doses of 4–6 mg of buprenorphine are recommended, and then increase the dose until 8–10 mg/day. After 2–3 days, the recommendation is to reduce the dose to 2 mg every 1–2 days until complete suppression. It is important to administer the first dose 24 h after the last heroin use, when the first withdrawal symptoms appear, in order to avoid a precipitated withdrawal.

In general, the use of long-acting opioids (such as methadone) is recommended in opioid detoxification, with a long and slow tapering, medical supervision, ancillary medications, and psychosocial treatment to improve the outcomes and reduce the risk of relapse (Amato et al. 2005a). However, there is a low rate of success in detoxification treatments with high prevalence of relapse in heroin use.

Rapid and ultrarapid protocols for detoxification are described. These inpatient protocols involve a rapid clonidine taper combined with a transition to narcotic antagonist treatment with naltrexone. Ultrarapid detoxification protocols require the use of general anesthesia or heavy sedation. A review of the evidence on rapid and ultrarapid detoxification concluded that the studies were inadequate because of the small number of subjects included, variations in protocols utilized, lack of randomized design and/or control groups, and lack of long-term follow-up (O'Connor and Kosten 1998). In addition, deaths and psychotic syndromes have been reported during the 16–40 h following ultrarapid detoxification (Kaye et al. 2003; Shreeram et al. 2001); for this reason alone, ultrarapid detoxification procedures cannot be recommended.

Continued Total Abstinence

Naltrexone is a full opioid antagonist used after complete opioid detoxification to maintain the total abstinence. Its high affinity for the mu-opioid receptor produces a blockade of the pharmacological effects of heroin during 24–48 h with 50 mg of naltrexone. To initiate naltrexone treatment, a naloxone test to assure the complete detoxification is recommended.

The main advantages of naltrexone include the following: decrease in opioid craving, can be administered in a standard outpatient office setting, and the absence of abuse potential. Also, it is well tolerated with few adverse effects, except for the risk of increase of liver enzymes. Despite all these advantages, naltrexone has shown low rates of efficacy, with poor retention and high relapse rates (Minozzi et al. 2011; Sullivan et al. 2006).

To improve the described problems with retention and relapse with naltrexone, a sustained-release formulation has been developed in the form of implants and

depot injections. A Cochrane review identified a trial where a dose of 384 mg of depot naltrexone was associated with better retention than placebo (Lobmaier et al. 2008). Another study performed in Russia (Krupitsky et al. 2011) also showed better rates of abstinence and retention in the depot naltrexone compared to placebo. Only one study has compared the efficacy of depot naltrexone versus methadone maintenance treatment (Lobmaier et al. 2010) in 46 volunteers in a prison setting. The study was randomized, and the results showed similar reductions in the use of heroin and benzodiazepines and criminality 6 months after prison release. In conclusion, depot formulations of naltrexone seem to be promising in order to improve outcomes in opioid dependence disorder in less well-integrated subjects with a strong motivation to become total abstinent. Oral naltrexone is a treatment option for patients also with a strong motivation to become total abstinent of all opioid agonists and very well integrated.

28.2.2.5 Opioid Maintenance Treatments

Maintenance treatment with opioid agonist stabilizes brain neurochemistry by replacing short-acting opioids with a long-acting opioid that has relative steady-state pharmacokinetics, such as methadone or buprenorphine.

Opioid agonist maintenance treatment is designed to have a minimal euphoric effect, blocks the euphoria associated with the administration of exogenous opioids, and eliminates the phenomenon of opioid withdrawal (Fiellin et al. 2006). The most frequently studied medications for maintenance treatment are methadone and buprenorphine and, to a lesser extent, (*R*)-methadone, levacetylmethadol (LAAM), sustained-release morphine, and diacetylmorphine (heroin).

28.2.2.6 Methadone Maintenance Treatments

In general, methadone maintenance treatment (MMT) is considered the first-line treatment for opioid dependence. MMT is the most widely used treatment for heroin dependence, and a great body of research exists that supports its effectiveness in the treatment of opioid dependence disorder. MMT has demonstrated its efficacy in retaining patients in treatment and decreasing illicit opioid use (Amato et al. 2005b; Farre et al. 2002), decreasing risk behaviors related to the HIV/sexually transmitted diseases (Marsch 1998), decreasing criminal behavior related with drug use (Dolan et al. 2005), reducing the risk of fatal overdose (Brugal et al. 2005), and improving health-related quality of life (Torrens et al. 1999).

Methadone dosing should be based on clinically guided dose titration. Usual maintenance dosage of methadone is 60–100 mg/day; some patients achieve abstinence or are free of withdrawal symptoms when treated with less than 40 mg/day of methadone. Some studies suggest that methadone doses of 60–100 mg/day or higher are more effective than lower doses for reducing or stopping illegal opiate self-administration in opioid-dependent patients. Regarding the duration of maintenance treatment, there are no clear recommendations; however, the literature shows better improvements with longer treatments, so the advice is to favor indefinite treatments and start the suppression when significant changes in lifestyle have been made (Calsyn et al. 2006; McLellan et al. 1997).

In spite of its well-established therapeutic efficacy, there is a large interindividual variability in outcome; between 30 % and 80 % of patients treated are poor responders to methadone treatment when retention in program and illicit opioid use are considered as the main measures of outcome (Bell et al. 2006; United States General Accounting Office 1990). Classically, the main strategies used to optimize the MMT programs have been focused in the characteristics of the MMT program, mainly in relation to the methadone provided (high vs. low methadone doses, abstinence-oriented programs vs. maintenance-oriented programs, etc.) and psychosocial programs offered (Ward et al. 1998).

The main problem associated with MMT has been described in the first part of this chapter and is related with an increased risk of QTc prolongation, needing a closer cardiological supervision (Fonseca et al. 2009; Krantz et al. 2009).

28.2.2.7 Buprenorphine and Buprenorphine–Naloxone Maintenance Treatments

Buprenorphine is a partial opioid agonist, with a ceiling effect for respiratory depression and with reduced abuse potential (Veilleux et al. 2010). Studies found buprenorphine to be therapeutically superior to naltrexone (Schottenfeld et al. 2008). When compared to placebo, buprenorphine at medium and high doses improved treatment retention and decreased opioid use (verified by urinalysis) (Mattick et al. 2008). However, when compared to methadone maintenance, methadone is more efficacious than buprenorphine in terms of treatment retention (Mattick et al. 2008; Hser et al. 2013).

A major concern with the use of buprenorphine the risk of diversion and misuse. Two strategies have been used to overcome this risk. The commercialization of buprenorphine in combination with naloxone (4:1 ratio, sublingual tablets containing buprenorphine 2 and 8 mg and naloxone 0.5 and 2 mg), and the use of deterrent formulations, as the soluble film, approved by the FDA in 2010 (sublingual film containing buprenorphine 2, 4, 8, or 12 mg and naloxone 0.5, 1, 2, or 3 mg) (Soyka 2012).

To initiate buprenorphine or buprenorphine–naloxone treatment successfully and to avoid a precipitated withdrawal, it is essential to determine that the patient is opiate-free for at least 24 h (in case of short-acting opiates) and observe the presence of opiate withdrawal symptoms. The recommended initial dose is 4 mg sublingually and should be administered at the clinic, and the patient should remain under observation for 2 h. Supplemental doses can be given if withdrawal symptoms persist, with a maximum recommended first-day dose of 8 mg. The dose can be raised in 2 to 4 mg increments over the next 2–3 days. Doses of 8–16 mg buprenorphine are superior to lower doses, and doses of 12–24 mg are preferable for maintenance treatment. Doses should not exceed a maximum single daily dose of 24 mg. Because of the ceiling effect, there is no pharmacological justification for daily doses over 32 mg.

Less than daily dosing can be used in patient using 8 mg/day or less. After a satisfactory stabilization has been achieved, the frequency of dosing may be decreased to dosing of every other day at twice the individually titrated daily dose. For example, a patient stabilized to receive a daily dose of 8 mg may be

given 16 mg on alternate days, with no dose on the intervening days. In some patients, after a satisfactory stabilization has been achieved, the frequency of dosing may be decreased to three times a week (e.g., on Monday, Wednesday, and Friday). The dose on Monday and Wednesday should be twice the individually titrated daily dose, and the dose on Friday should be three times the individually titrated daily dose, with no dose on the intervening days. However, the dose given on any 1 day should not exceed 24 mg.

The main advantages of buprenorphine compared to methadone maintenance treatment are the lower risk of fatal respiratory depression during intoxication, the quick induction to full doses, its cardiac safety because it has no effect on the QTc interval, the lower risk of interactions, and the destigmatization of patients compared to methadone.

28.2.2.8 (*R*)-Methadone Maintenance Treatment

(*R*)-methadone (or L-methadone or Polamidon®) is the active component of the racemic methadone, and it is used in Germany as the maintenance treatment of opioid dependence disorder. As described previously, (*R*)-methadone shows more affinity of the mu receptors and has more analgesic potency than (*R,S*)-methadone (Eap et al. 2002). Efficacy studies show no differences between the (*R*)-enantiomer and the racemate (Judson et al. 1976; de Vos et al. 1998).

As the cardiac side effects of methadone reside in the (*S*)-enantiomer, the substitution of the racemate by the (*R*)-methadone has demonstrated a reduction in the QTc interval (Ansermot et al. 2010), reducing the risk of sudden death in methadone-maintained patients. Unfortunately, the direct costs of the treatment with (*R*)-methadone are much higher than the use of the racemate.

28.2.2.9 LAAM Maintenance Treatments

LAAM, another mu full agonist, is associated with the suppression of heroin use. Its long half-life allows an administration pattern of thrice weekly. Stabilization doses vary from 40 to 140 mg. However, LAAM maintenance treatments present more dropouts, likely due to increased adverse events (Clark et al. 2002). Moreover, LAAM has been excluded from treatments due to the possibility of a fatal ventricular arrhythmia ("torsade de pointes") (Clark et al. 2002; Wedam et al. 2007).

28.2.2.10 Sustained-Release Oral Morphine (SROM) Maintenance Treatment

In the last years, maintenance treatment with SROM for opioid dependence disorder had captured more interest. At this moment, SROM is available as an alternative for methadone in Austria, Slovakia, Slovenia, Bulgaria, Luxembourg, and exceptionally France (Jegu et al. 2011). A systematic review (Jegu et al. 2011) and a Cochrane review (Ferri et al. 2013) have been published in recent years. At this point, the body of evidence is not enough to assess the effectiveness of SROM for opioid maintenance; available data shows that retention rates are similar to those of methadone treatments; most of the studies showed that quality of life, withdrawal symptoms, craving, and additional drug consumption improved with SROM;

however, most of the studies were not controlled with other maintenance treatments. Its main advantage over methadone treatments is the lower risk to induce prolongation of the QTc interval (Fredheim et al. 2006), allowing an easy switch from methadone to SROM in case of detection of a QTc interval above 500 ms.

The major concerns with SROM treatments are the risk of misuse and diversion and the severe adverse events, such as overdose (Beer et al. 2010), described in countries such as Austria.

28.2.2.11 Diacetylmorphine Maintenance Treatments

Diacetylmorphine (diamorphine, heroin) has also been studied in patients with a history of unsuccessful agonist treatment in specific programs in a few countries. Various studies and a Cochrane collaboration study have been published in order to analyze the efficacy and feasibility of diacetylmorphine maintenance treatments (Uchtenhagen 2011; Ferri et al. 2011). In general, heroin treatments have been implemented with good acceptance by patients and public opinion. The treatment has been usually prescribed alongside methadone and has demonstrated an increase in treatment retention and reduced engagement in illegal activities in patients who previously failed in other maintenance programs (Strang et al. 2010; Ferri et al. 2011). Diacetylmorphine has been used in these programs by injectable (intravenous), smoked, and oral route.

The main problem is related with the rate of serious adverse events, mainly the risk of overdose; for that reason, the treatment is only recommended in patients refractory to other substitution treatments and should be provided in settings with proper medical assistance (Ferri et al. 2011).

28.2.2.12 Psychosocial Treatments in Opioid Dependence

Psychosocial treatments are those that use any psychological or social strategy to achieve an improvement or a behavioral change. Interventions at a social level include assistance with basic needs such as food, clothing, accommodation, and employment, as well as basic health care, friendship, community, and the pursuit of happiness.

Opioid treatment guidelines (as the WHO guidelines 2009) recommend the use of psychosocial treatments. Interventions at a psychological level range from unstructured supportive psychotherapy and motivational interviewing techniques to highly structured psychological techniques.

The main psychological strategies in opioid dependence are cognitive behavioral therapy (CBT) and contingency management. Cognitive approaches primarily aim to change addictive behaviors by changing faulty cognitions that serve to maintain behavior or by promoting positive cognitions or motivation to change behavior. Behavioral approaches aim primarily to modify behaviors underpinned by conditioned learning, that is, by classical and operant conditioning.

Contingency management rewards or punishes specific types of behaviors using a structured, transparent approach that increases learning of desired behaviors.

In terms of social interventions, the main interventions used in addiction disorders are as follows: vocational training, which includes a range of programs

designed to help patients find and retain employment; housing services that can vary from group accommodation for the homeless to more stable, affordable, long-term accommodation; the referral to participate in activities, such as enjoying leisure activities of their choice; and self-help groups, which, in the context of opioid dependence, are voluntary, small-group structures formed by peers to assist each other in their struggle with opioid dependence. Usually abstinence oriented, they often provide both material assistance and emotional support and promulgate an ideology or values through which members may attain a greater sense of personal identity. Social skills training refers to methods that use the principles of learning theory to promote the acquisition, generalization, and durability of skills needed in social and interpersonal situations. Training should take place in the context of real everyday life experiences, not in closed, unrealistic settings.

In opioid dependence, the efficacy of psychosocial interventions has little evidence due to the difficulty in the design of controlled trials. Also, there is scarce knowledge about the effectiveness of psychosocial interventions alone or in combination with pharmacological strategies and which intervention is the most effective. There are studies recommending counseling (Grönbladh and Gunne 1989), relapse prevention, and motivational interview techniques (Pollack et al. 2002). Also, family therapy (Stanton and Shadish 1997) and psychoanalytic psychotherapy have been shown to have some benefits in the treatment of opioid dependence disorder (Woody et al. 1987).

A Cochrane collaboration study (Mayet et al. 2010) addressed the issue of the efficacy and acceptability of psychosocial interventions alone for treating opiate use disorders. Only randomized controlled trials comparing psychosocial interventions alone versus pharmacological intervention, placebo, or no intervention were selected. The psychosocial interventions evaluated included the following: contingency management, brief reinforcement-based intensive outpatient therapy coupled with contingency management, cue exposure therapy, alternative program for methadone maintenance treatment program (MMTP) dropouts, and enhanced outreach counseling program. The main findings were that both enhanced outreach counseling and brief reinforcement-based intensive outpatient therapy coupled with contingency management had significantly better outcomes than standard therapy regarding relapse to opioid use, re-enrolment in treatment, and retention in treatment. At 1-month and 3-month follow-up, the effects of reinforcement-based intensive outpatient therapy were not sustained.

A parallel review (Amato et al. 2011) was performed to evaluate the effectiveness of any psychosocial plus any agonist maintenance treatment versus standard agonist treatment for opiate dependence. In this review, 35 studies and 4,319 participants were included, evaluating 13 different psychosocial interventions. Comparing any psychosocial plus any maintenance pharmacological treatment to standard maintenance treatment, results do not show benefit for retention in treatment and outcomes. Surprisingly, there were no differences also for contingency management approaches; the authors stated that the short duration of the trials could interfere in the results.

28.3 Conclusion

In this chapter the authors have presented the main pharmacological characteristics of the most common opioids involved in drug addiction and addiction treatment (both opioid addiction and alcohol addiction) and the present alternatives for the treatment of the opioid dependence disorder. The majority of research until few years ago has been focused on the effects mediated by mu-opioid receptors. However, in recent years most interest has been shifted to the effects on the kappa-opioid receptors. The kappa system including its natural ligand (dynorphin) interacts with dopaminergic pathways and modulates the reward, mood, and stress processes by its effects on the hypothalamic–pituitary–adrenal (HPA) axis. Kappa agonism usually produces aversion and dysphoria; in rats, depressant-like effects after the administration of kappa agonists have been described; on the other hand, the anhedonic symptoms that appear after stress exposure or cocaine withdrawal are ameliorated with kappa antagonists (Shirayama et al. 2004; Chartoff et al. 2012). Researchers postulate that increased endogenous kappa/dynorphin activation could result in neuropsychiatric adverse events (Butelman et al. 2012), explaining in part the high rates of psychiatric comorbidity in the addicted patients (Tejeda et al. 2012). From a therapeutic point of view, the use of kappa partial agonists could provide a stable counter-modulatory tone to dopaminergic urges and cause a relative blockade of excessive or fluctuating kappa/dynorphin tone; both effects may mitigate against relapse and reescalation (Butelman et al. 2012).

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Buprenorphine in the Treatment of Opioid Addiction: The French Experience

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Abstract

Buprenorphine provides a number of benefits and was registered as a medication for opiate addiction treatment by the French health authorities as early as 1995. All registered medical doctors may prescribe this treatment without requiring any supplementary educational program or special licensing. The French health organizations enable a substantial care within primary care settings through medical and social support and through the possibility of supervised dispensing through pharmacy services. Overall, 26 % of French physicians prescribe buprenorphine to 75 % of overall patients in buprenorphine maintenance treatment. Buprenorphine maintenance treatment for problem heroin users has been associated in France to consistent public health, social, individual and economic benefits; might be contingent upon characteristics of the French health and social services system; and may not necessarily be generalizable as is to other areas of the world.

29.1 Introduction

It has been argued that the pharmacology of buprenorphine provides a number of benefits (Cowan and Lewis 1995). Like methadone, buprenorphine is a long-acting oral medication used to stabilize patients with opiate addiction and reduce or prevent craving. Unlike methadone its long duration of action is not due to a long plasma half-life but to its high affinity for the mu receptor. Buprenorphine also differs from methadone in that it is a partial agonist at the mu receptor, making overdose less likely. Cessation of the drug is associated with milder levels of withdrawal distress; and the long duration of its action permits more flexible dispensing options such as every other day administration. Based on our experience of using buprenorphine for opioid dependence with dispensing in community pharmacies in France since 1986 (Auriacombe et al. 1992, 1994) and that of others, buprenorphine was registered as a medication for opiate addiction treatment by the French health authorities as early as 1995. All registered medical doctors may prescribe this treatment without requiring any supplementary educational program or special licensing, exactly as for most medications. The French experience since 1995 in using buprenorphine and training and regulating family physicians is informative for worldwide efforts to facilitate opiate problem users' access to treatment (Auriacombe et al. 2004). Many contextual factors contribute to buprenorphine treatment in France and have to be taken in consideration to understand the overall outcomes and possible generalization to other regions of the world. These include the role of buprenorphine's pharmacology vs. that of methadone, the involvement of GPs over specialist practitioners, the importance of office-based settings vs. center-based settings, and issues of funding and health insurance. All these play a role in the overall outcome of "buprenorphine treatment in France" (Fatseas and Auriacombe 2007).

29.2 The French Experience

29.2.1 "Buprenorphine Treatment" in the French Context

29.2.1.1 General Characteristics of the French Health System

The overall organization of the healthcare system is an important possible contributor to buprenorphine treatment in France. The social security system acts as a universal medical insurance that covers over 90 % of the population, regardless of their economic situation, legal status, or nationality (Fielding and Lancry 1993). This facilitates the treatment of marginalized individuals. A general practitioner is paid a fixed price for an office visit, regardless of duration or frequency. Ordinary consultations are reimbursed at a 65 % replacement level. However, if the patient has a chronic illness, reimbursement covers 100 %, and the payment can be made directly from social security to the general practitioner. Because opiate dependence may qualify as a chronic illness in the French healthcare system, payment is fully covered by social security. In addition, there is a dense psychosocial support service funded by local authorities at no charge to those in need. Further, patients with opiate dependence can be treated in special substance abuse treatment centers supported by social security funds. The medication itself can be dispensed and ingested at the pharmacy under the supervision of the pharmacist daily, if prescribed. In this context, pharmacists play a crucial role in dispensing of treatment, in monitoring clinical improvement of patients, and in informing the prescriber about any difficulties. Overall, the French health organizations enable a substantial care within primary care settings through medical and social support and through the possibility of supervised dispensing through pharmacy services.

29.2.1.2 Methadone and Buprenorphine Prescription Regulations in France

The difference in regulation contributes to the specific French increased number of buprenorphine-maintained patients in comparison to methadone-maintained patients in contrast to most other countries worldwide. Only physicians working in state-licensed substance abuse clinics or hospitals can initiate a methadone prescription that is initially dispensed only on-site. Urine testing is compulsory. Once the initial prescriber has determined that the patient is stabilized, clinical management of the patient and methadone prescription may be transferred to any medical doctor. At that point, dispensing may be done from any pharmacy in the same manner as for buprenorphine. In contrast, buprenorphine's regulation is very different. Any physician working in office-based settings can prescribe buprenorphine, and any pharmacy can provide the medication. There is no requirement for any type of specific training. The maximum duration of a buprenorphine prescription is 28 days, and the maximum number of take-home doses is seven. However, a physician can override this rule by requesting that the pharmacist either provide daily supervised dosing of buprenorphine or dispense up to 28 days of take-home doses. There is no regulatory requirement for urine testing.

Overall, 26 % of French physicians prescribe buprenorphine to 75 % of overall patients in buprenorphine maintenance treatment (Cadet-Taïrou and Chollet 2004). These physicians are more often members of a healthcare network, trained for drug maintenance treatments, which may reflect special motivation and involvement in management of opiate-dependent subjects (Feroni et al. 2004). Hence, although there are no regulatory training requirements prior prescribing buprenorphine, the majority of patients are receiving prescriptions from physicians that have had extra training in addiction medicine and are involved in community-based treatment networks.

29.2.2 Main Outcomes of Buprenorphine Treatment in France

Buprenorphine maintenance treatment for problem heroin users has been associated in France to consistent public health, social, individual, and economic benefits (Fédération française d'addictologie 2004).

Studies have reported a significant decrease of heroin use and injection practice and an improvement in the social conditions of those in treatment (Duburcq et al. 2000; Bilal et al. 2003). Data also suggest among those that inject a decrease of risk-taking behavior related to injection, such as needle and paraphernalia sharing (Cadet-Taïrou and Chollet 2004). Similarly, in both retrospective and prospective studies (De Ducla et al. 2000; Duburcq et al. 2000; Fhima et al. 2001) carried out among drug-dependent outpatients treated by general practitioners, results indicate a significant decrease of both heroin and benzodiazepine use over time in treatment and that persistent benzodiazepine use among buprenorphine-treated individuals was related to less supervised dispensing and lower buprenorphine dosage. A study documented particularly the positive impact of buprenorphine on the social conditions of patients (Bilal et al. 2003), indicating that all markers of social vulnerability assessed through standardized questionnaires (employment, housing, social insurance, days of in-patient treatment related to drug consumption, and number of convictions) were improved after a 6-month period with buprenorphine.

Another consistent impact is the dramatic decrease of the reported overdose deaths since the development of buprenorphine treatment. In France, overdose deaths are registered by the police (Office Central pour la Répression du Trafic Illicite des Stupéfiants 1999). The causes of such deaths are determined on the basis of on-site evidence. This source of information is, as in most countries, considered to be an underrepresentation of true overdoses. Since country-specific methodological, legal, and political issues affect this reporting, the data cannot be compared between different countries. But since the monitoring system has been unchanged for many years, it is appropriate to compare the development of overdoses from year to year within France (Auriacombe et al. 2001). In this regard, the French overdose mortality monitoring system shows a consistent decrease in overdose deaths since the introduction of buprenorphine. The number of overdose deaths declined by 79 %, while the overall number of opiate-abusing individuals in either buprenorphine (80 %)

or methadone (20 %) treatment increased by over 95 % (from less than 2,000 per year to over 60,000 per year) within the 5 years following the introduction of buprenorphine and the involvement of general practitioners. Some authors have suggested that the increase in buprenorphine-treated individuals is the major cause for the decline in overdose deaths (Lepere et al. 2001). However, it should be acknowledged that during this same time, there was a development of syringe exchange programs, an increased availability of center-based methadone treatment, and a possible overall change in attitude toward intravenous drug users by health providers (Emmanuelli and Desenclos 2005).

29.2.3 Problems Related to Buprenorphine Treatment in France

29.2.3.1 Mortality Related to Buprenorphine

Deaths due to buprenorphine misuse are very rare, and it is thought that the risk of overdose is lower with buprenorphine than with other opiates because of its agonist–antagonist pharmacological characteristics and because its usual administration is sublingual.

However, some authors have reported deaths in which buprenorphine was considered as a contributing or causal factor (Tracqui et al. 1997, 1998; Reynaud et al. 1998a, b; Kintz 2001). In all of these cases, buprenorphine was found by systematic analytical toxicology regardless of clinical context information very often lacking. Benzodiazepines and other central nervous system respiratory depressants were almost all the time identified in addition to buprenorphine: benzodiazepines, cannabis, neuroleptics, and alcohol. A causal role for buprenorphine in most of these deaths is questionable. It is thought that the risk of overdose is highest with intravenous injection and concomitant use of alcohol and sedatives.

Perhaps what is most relevant is to compare overdoses between buprenorphine treatment and methadone treatment over the same time frame (Auriacombe et al. 2001), as the alternative to buprenorphine is not no treatment but methadone treatment. For the 1995–1998 period, the risk of death attributed to methadone was considerably higher than that attributed to buprenorphine – in fact, over ten times higher during the same 4-year period. Comparing data on the number of deaths related to methadone misuse and the number of deaths related to buprenorphine misuse, buprenorphine appears to be associated with a lower risk than methadone (Observatoire français des drogues et des toxicomanies 2005). Noteworthy, this has now been reported in other countries (Bell et al. 2009; Soyka et al. 2011).

29.2.3.2 Diversion and Abuse Related to Buprenorphine

The diversion of buprenorphine to the black market is likely to concern marginalized populations, who may obtain it from multiple providers. French surveys from medical insurance database indicated that around 10–20 % of patients collect prescription from more than one provider and/or filled prescriptions in several

pharmacies, whereas 80 % of patients in treatment only see one prescriber on a regular basis and go to only one pharmacy (Damon et al. 2001; Vignau et al. 2001; Thirion et al. 2002). Several factors might be involved in the practice of "doctor shopping." First, the French health system and insurance policy make it easier by allowing people whatever the medication to receive care and treatment from different general practitioners. Indeed, the French healthcare system is centered on the patient who determines when, where, and how frequently to attend heath providers. Another factor potentially involved is subtherapeutic buprenorphine dosing as data suggest that doctor shopping is less common when physicians prescribe 8 mg/day of buprenorphine or more (Feroni et al. 2005; Carrieri et al. 2006).

The diversion of buprenorphine via the intravenous route varies widely between studies. Diversion poses the problem of the risk-taking behaviors related to injection, medical complications (particularly an increased risk of liver toxicity), and the association to other substances (with possible increased risk of overdose). Some studies report that 11 % or less of outpatients in treatment have used buprenorphine intravenously (Cadet-Taïrou and Chollet 2004). Studies carried out among specific populations have revealed that the proportion of buprenorphine misusers is higher among patients of low-threshold services (up to 41 %) (EMCDDA 2005). Misuse of buprenorphine is also reported to be quite common among homeless people living in urban regions (Blanchon et al. 2003). Specific risk factors for buprenorphine injection in treatment settings may be as follows: being a polydrug user, being in precarious economic conditions, and having an insufficient dose of buprenorphine (Blanchon et al. 2003). Interestingly, since 2005, a consistent decrease in buprenorphine injection is reported (EMCDDA 2005; Cadet-Taïrou et al. 2010). This seems to be parallel to shared concerns by health regulatory authorities and individual clinicians.

Among regular opiate users, buprenorphine's pharmacology makes it theoretically unlikely to be a substance of abuse, and indeed, from some reports, it appears that out-of-treatment opiate users are not interested in buprenorphine as a recreational drug. Despite the relatively easy access to buprenorphine, it appears that the large majority of French out-of-treatment opiate users are not interested by buprenorphine and prefer heroine when available. One study (Moatti et al. 2001; Obadia et al. 2001) reported on the use of buprenorphine by individuals who were interviewed while they were accessing clean syringes from syringe exchange programs, vending machines, or community pharmacies. In this intravenous drug-using population, 57 % reported that they injected buprenorphine at least once over the past 6 months. However, the majority (60 % of those having used buprenorphine intravenously at least once and 34 % of the total sample) reported being regular injectors of heroin and cocaine but injecting buprenorphine only occasionally. The remaining 40 % of buprenorphine injectors (24 % of the total sample) declared having used only buprenorphine over the past 6 months; interestingly, the majority of those declared being in buprenorphine treatment. This group of in-treatment buprenorphine injectors (compared to occasional out-of-treatment buprenorphine injectors) declared less needle-sharing activities and polydrug use. The confusing factor preventing a clear conclusion from this study's data is the heterogeneity of the studied population.

The majority of patients were out-of-treatment, and they injected primarily heroin and cocaine as well as buprenorphine. A significant minority was in buprenorphine treatment and only injected buprenorphine. On all variables, this latter group had better adjustment: more employment, less needle sharing, and less polydrug use. Thus, the simple prevalence of intravenous diversion may not be the best indication of the overall effectiveness of buprenorphine treatment. This study only documents the existence of buprenorphine abuse, but even this population of regular buprenorphine intravenous abusers appears to be doing better than those that use less or no buprenorphine. Similar results with similarly limited information were found in a study focusing only on syringe exchange programs (Valenciano et al. 2001). Two studies (Fontaa and Bronner 2001; Franques et al. 2003) have compared the use of the intravenous route in both methadone- and buprenorphine-treated individuals. Interestingly, the prevalence of use of the intravenous route was similar in both populations, about 20 %. However, the buprenorphine patients were more likely to inject their own prescribed buprenorphine, whereas those methadone patients who injected were more likely to inject heroin and cocaine but not methadone, which is only available as a difficult-to-inject syrup at the time.

Finally, cases of buprenorphine use as first drug of abuse or dependence have been reported in France (Escot and Fahet 2004) in low-threshold programs. In these settings, buprenorphine as the first opiate used concerned 6 % of the subjects, and buprenorphine as the first opiate used with a diagnosis of dependence, 12 % of the subjects. These buprenorphine-dependent subjects were more likely to have a problematic associated use of alcohol or benzodiazepines and reported more often to use buprenorphine for its anxiolytic or psychotropic effect, in order to relieve social or psychological difficulties than just as a recreational alternative.

29.2.4 What Is Next?

Increasing quality of treatment services and decreasing collateral damage related to such services are important challenges for health authorities and individual clinicians. It is currently an important issue in the French situation for the treatment of opiate-addicted patients with buprenorphine office-based treatment and methadone center-based treatment. From a public health perspective, it is likely difficult to imagine doing any better when comparing with other regions in Europe, North America, and Australia. In a very cost-effective manner (Kopp et al. 2000), more than two-third of the total estimated number of opiate problem users are in either buprenorphine or methadone treatment, and the large majority of these receive treatment from a general practitioner. Since these important changes, over the past 10 years, opiate-related overdose mortality, HIV drug-related prevalence, and drug-related crime have dropped dramatically (Emmanuelli and Desenclos 2005). From this public health and societal perspective, major changes in regulations are not easy to imagine. However, from an individual clinical perspective, cases of misuse of buprenorphine by the intravenous or intranasal routes and associated damage are of legitimate concern as well as issues related to the leaking of

buprenorphine to the black market and possible clinically inappropriate use. Understanding some of the determinants of these individual behaviors, such as patient motivation for use, can give insight as to how to do better (Fatseas et al. 2009).

Within the French treatment system, an important variable that may influence office-based treatment efficacy could be the frequency with which supervised – as opposed to take-home – doses of buprenorphine are administered. In a study, 202 patients were assigned quasi-randomly to daily supervised dosing for either 2 weeks, 3 months, or 6 months, after which dosing was on a weekly schedule (Auriacombe et al. 2002). Results from this study showed that retention in treatment at the 6-month follow-up was highest for those patients in the 6-month daily supervised dosing group (80 %) and lowest for those patients in the 2-week daily supervised dosing group (46 %). Rates of opiate-positive urine samples were lowest for the 6-month daily supervised dosing group, compared to the 3-month daily supervised and 2-week daily supervised groups. Finally, average daily buprenorphine doses at the 6-month assessment were similar for the three groups. These results suggest that initial efficacy for office-based buprenorphine treatment may be enhanced by a more closely supervised dispensing of medication and that this may be acceptable to patients.

Finally, data strongly suggest that prescription practices (single daily and individually titrated dosing) and prescribers' attitudes and beliefs about drug-dependent patients are closely associated to general treatment outcomes and patient compliance and behavior (De Ducla et al. 2000; Feroni et al. 2005).

29.3 Conclusion

As evidenced by the French example, buprenorphine maintenance treatment for problem opiate users can be feasible and safe through office-based prescriptions. This "French experience" is unparalleled in its rapid growth, and even though there is some level of diversion and continued intravenous use, it is also fair to say there are very significant societal and individual benefits. In addition there is evidence that some clinical attitudes of physicians might favor diversion more than patient characteristics. Particularly buprenorphine underdosage, the lack of toxicological monitoring of drug use, and the lack of supervised dispensing in pharmacies have been shown to represent risk factors for diversion and misuse. In the current context of the French experience, strategies to reduce buprenorphine diversion and misuse should focus on quality of treatment provision more than on regulatory changes. Among these strategies, helping health professionals, especially general practitioners, may play a crucial role allowing specific training in addiction treatment and facilitating interactions between primary care settings and specialized facilities. Finally, it is important to keep in mind that some of the public health benefits seen during the time of buprenorphine expansion in France might be contingent upon the characteristics of the French health and social services system and may not necessarily be generalizable as is to other areas of the world.

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Buprenorphine Implants: Review of Clinical Studies

30

Martin S. Mumenthaler and Katherine L. Beebe

Contents

Abstract

To address shortcomings that opioid dependence treatment with daily sublingual buprenorphine doses has, such as medication adherence, buprenorphine abuse and diversion, and accidental exposure to children, Buprenorphine Implants (BI) have been developed as a subdermally implantable formulation of buprenorphine with 6-month duration of action. A New Drug Application has been submitted for this novel medication and is currently under review by the FDA. This chapter provides a summary of the clinical studies of BI to describe the formulation and its pharmacokinetics, efficacy, and safety. The data showed superiority of BI to Placebo Implants (PI) and non-inferiority to sublingual

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buprenorphine in primary (urine samples negative for opioids) and secondary outcome measures, demonstrating safety and efficacy of BI for the maintenance treatment of opioid dependence.

30.1 Introduction

Addiction to heroin and prescription opioids represents a worldwide health and social crisis. Methadone maintenance has been established as a successful treatment for opioid dependence, reducing morbidity, mortality, and the spread of infectious diseases (Marsh 1998) but is restricted in the USA to specialty clinics and has a risk of mortality with overdose (Luty et al. 2005). The use of buprenorphine, a partial opioid receptor agonist which can be prescribed in office-based physician practice in the USA, has significantly increased in the treatment of opioid dependence in the last decade, and buprenorphine is established as a safe and efficacious treatment. However, the sublingual (SL) route of delivery has several shortcomings. First, it requires strict subject dosing compliance: one missed dose may allow cravings and withdrawal symptoms to increase to the point at which the subject seeks illicit drugs. More specifically, poor medication adherence is the leading cause of relapse, treatment failure, re-involvement in criminal activity, and mortality. Second, in some countries, including the USA, the patient is in control of his/her dosing, and a conscious decision to discontinue buprenorphine treatment for the short term in anticipation of exposure to illicit drugs can easily occur. Third, buprenorphine SL tablets can easily be diverted for illicit use, a growing public health issue in the USA, or accidentally ingested after misidentification (Winstock et al. 2008; Chandler et al. 2009). Fourth, frequent visits to the clinic or pharmacy are required, limiting subject independence and requiring significant medical staff time and cost. And fifth, although the SL formulation is thought to reduce the euphoria-inducing effects of buprenorphine by slowing down its absorption and uptake to the brain, plasma concentrations initially peak steeply with each dose, leading some subjects to experience withdrawal symptoms between doses. These shortcomings represent significant obstacles to realizing the full potential of buprenorphine as an important pharmacotherapy for the opioid-dependent population and for society as a whole, and they provided the rationale to develop Buprenorphine Implants (BI).

Buprenorphine Implants are a subdermally implantable formulation of the active ingredient buprenorphine, intended to provide continuous delivery of buprenorphine for 6 months for maintenance treatment of opioid dependence following outpatient induction with daily SL buprenorphine. It minimizes access to buprenorphine and the potential for diversion and misuse. This novel formulation is not yet FDA approved and a New Drug Application (NDA) is currently under review by the FDA.

The present review will summarize the Buprenorphine Implants clinical program which consisted of six studies designed to evaluate the safety and efficacy of BI for maintenance treatment of opioid dependence.

30.2 Clinical Studies of Buprenorphine Implants

30.2.1 Buprenorphine Implants Formulation

Buprenorphine Implants are subdermal implants containing 80 mg buprenorphine hydrochloride USP in an ethylene vinyl acetate copolymer (EVA) matrix. Each implant measures 26 mm in length, 2.5 mm in diameter, and 112 mg in weight.

BI provide a long-acting (6 months) treatment for opioid dependence that should be used as part of a complete treatment program to include counseling and psychosocial support. Four implants are administered subdermally in the inner side of the patient's upper arm during an in-office procedure, and patients may receive a fifth implant if an increased dose is required. By the end of the sixth month, BI must be removed and may be replaced by new implants in the opposite arm at the time of removal, if continued treatment is desired. The matrix formulation of the implants results in a steady-state delivery of buprenorphine that maintains a stable plasma level of the drug for 6 months.

30.2.2 Buprenorphine Implants Clinical Program

To test the clinical efficacy of BI, two multicenter, double-blind, Placebo Implant-controlled studies (PRO-805 and PRO-806) with one containing an exploratory open-label active comparator arm (PRO-806) and two open-label extension studies (PRO-807, PRO-811) were conducted. Study 806 was partially funded by a grant from NIDA. Two pharmacokinetic studies also provided supportive efficacy and safety information (studies TTP- 400-02-01 and PRO-810). The six studies are summarized in Table 30.1.

30.2.3 Buprenorphine Implants Pharmacokinetics

During all six clinical studies, plasma samples were collected for measurement of buprenorphine concentrations. Figure 30.1 shows the six individual mean plasma concentration-time curves of these studies. The buprenorphine plasma concentration profile after subdermal implantation of BI shows an expected initial peak on the first day followed by a gradual concentration decrease over 4 weeks to a more constant, low plasma level ("steady state") that is then maintained within an efficacious range for the duration of the 6-month treatment. In a 24-week, open-label, sequential dose group study (TTP-400-02-01), steady-state plasma buprenorphine concentrations in the 2- and 4-implant groups were approximately dose linear, and the within-patient variability during the plateau phase was low, with coefficients of variation (CVs) ranging from 11 % to 20 % for patients who received two implants and 9–20 % for patients who received four implants.

In the single crossover, open-label, relative bioavailability PK study (PRO-810), comparing the reference drug Suboxone® SL tablets (16 mg/day) to four 80 mg BI,

Table 30.1 Clinical development program

Study number	Description
TTP-400-02-01	Phase 1/2 PK study of 2 or 4 Buprenorphine Implants in adults with heroin dependence
PRO-805	Randomized (2:1), double-blind, Placebo Implant-controlled[a] phase 3 study of the safety and efficacy of buprenorphine for maintenance treatment of opioid dependence in adults
PRO-806	Randomized (2:1:2), double-blind, Placebo Implant- and active-controlled[a] phase 3 study of the safety and efficacy of buprenorphine for maintenance treatment of opioid dependence in adults
PRO-807	Open-label extension study (PRO-805) to evaluate safety of serial 6-month treatment periods
PRO-810	Relative bioavailability PK study comparing buprenorphine with SL buprenorphine, no rescue medication used
PRO-811	Open-label extension study (PRO-806) to evaluate safety of serial 6-month treatment periods

TTP-400-02-01 was conducted in Australia; all other studies were conducted in the USA
[a]Patients in all treatment groups were allowed to receive SL buprenorphine/naloxone as rescue therapy

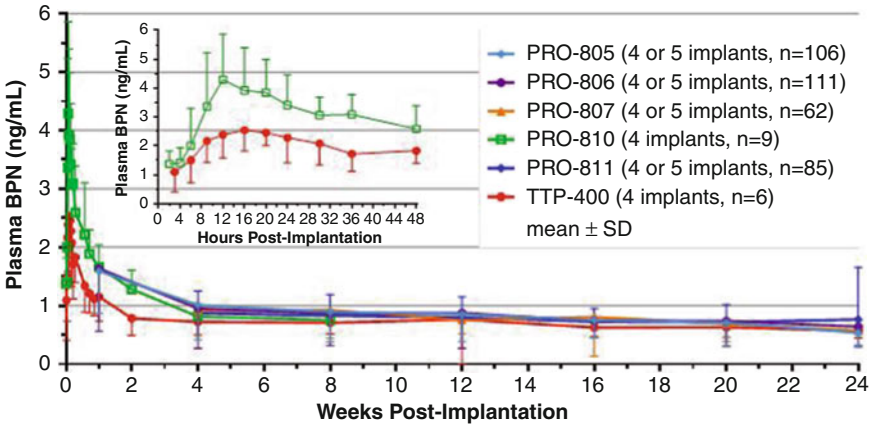

Fig. 30.1 Plasma buprenorphine concentrations over time, individual studies

buprenorphine concentrations in the BI group at steady state were 38–48 % less than trough concentrations during SL buprenorphine dosing on Days 2 and 1 (i.e., 2 days and 1 day before the transition to the four implants). At steady state, daily exposure (area under the plasma concentration-time curve from time 0 to 24 h) in the BI group was approximately 70 % lower than that in the SL buprenorphine group. In all phase 3 efficacy studies, mean steady-state plasma buprenorphine concentrations were similar at approximately 0.5–1 ng/mL.

30.2.4 Clinical Safety of Buprenorphine Implants

The safety evaluation of BI, which included analysis of adverse events (AEs), clinical laboratory assessments, ECG evaluations, and vital signs, showed that BI were well tolerated and posed minimal safety risks through two 24-week periods in adults with opioid dependence. The safety observations in all phase 3 studies were consistent with the known profiles of marketed buprenorphine forms and with the safety of EVA subdermal implants that are in wide clinical use. Further, the non-implant site safety profile observed with BI was unremarkable and fundamentally similar in the BI, Placebo Implant (PI), and SL buprenorphine groups, with discrete events occurring more frequently in one group or another with no systematic pattern. No unexpected systemic AEs occurred, and implant site AEs were generally minor, easily managed, and rarely leading to study discontinuation. The most common non-implant site adverse events (in >5 % of patients) that occurred at a higher incidence in the BI group than in the PI group were headache, nasopharyngitis, nausea, constipation, URI, back pain, toothache, anxiety, upper abdominal pain, vomiting, oropharyngeal pain, fatigue, and cough. The most common implant site adverse events (in >5 % of patients) in the first double-blind study (PRO-805) were pruritus, pain, erythema, hemorrhage, edema, hematoma, and scar. With modified procedures introduced in study PRO-806, the implant site adverse events decreased substantially and only pain and hematoma were reported in more than 5 % of patients. Collectively, the data from the safety program indicate that BI are safe and well tolerated for maintenance treatment of opioid dependence.

30.2.5 Clinical Efficacy of Buprenorphine Implants

All clinical studies evaluated similar patient populations. This chapter will focus on the two multicenter, placebo-controlled 24-week pivotal trials (PRO-805, PRO-806) and will provide only brief descriptions of efficacy measures in the open-label extension. The primary efficacy objective was to determine whether BI reduced illicit opioid use relative to PI, and the primary efficacy measure was the proportion of urine samples negative for opioids collected from weeks 1 to 24 (with missing urines imputed as positive), incorporating patient self-reported opioid use, and examined as a cumulative distribution function (CDF). Additional efficacy measures included study completion, Clinical Opiate Withdrawal Scale (COWS), Subjective Opiate Withdrawal Scale (SOWS), Visual Analog Scale (VAS) for opioid cravings, Clinical Global Impressions scores for self and observer (CGI-self, CGI-observer), and supplemental SL buprenorphine use.

In studies PRO-805 and PRO-806, patients underwent an outpatient induction period with SL buprenorphine or buprenorphine/naloxone tablets (12–16 mg/day) and were then randomized to either receive four BI or four Placebo Implants. All patients could receive supplemental rescue medication (SL buprenorphine/naloxone) if they met one or more of the following pre-specified criteria: (a) withdrawal

symptoms with a score of >12 on the COWS, (b) cravings with a score of >20 mm on the opioid cravings VAS, and (c) patient request for rescue medication deemed appropriate by the investigator. Patients who required supplemental SL buprenorphine/naloxone ≥3 days per week for two consecutive weeks or ≥8 days of supplemental SL buprenorphine/naloxone over four consecutive weeks received one additional implant. Patients returned to the clinic thrice weekly for urine toxicology screening and other data collection and attended twice-weekly manual-guided drug counseling during study weeks 1–12 and weekly counseling during weeks 13–24. A more detailed description of the study methodology can be found in (Ling et al. 2010).

30.2.5.1 Primary Efficacy Measure

To aid interpretation of the primary analysis using CDF, Fig. 30.2. first illustrates the results for the percentage of opioid-negative urine samples from weeks 1 to 24 as mean and median values. In both studies, the BI group had significantly greater mean and median proportions of opioid-negative urines than did the PI group.

The median values displayed in Fig. 30.2 are also illustrated in the CDF display as the "x" values corresponding to 50 % of patients in Fig. 30.3 below.

The primary analysis was a stratified Wilcoxon rank sum test of the CDF of the percentage of urine samples that were negative for illicit opioids from weeks 1 to 24. Figure 30.3 shows that BI were superior to PI in both studies.

To explore whether efficacy varied over the 24-week treatment period, the CDF of opioid-negative urine samples was applied to various time periods (weeks 1–16, 17–24, 5–24, 9–24). For each time period, the differences between the BI and PI groups were nominally statistically significant (P-values ranging from <0.0001 to 0.0347), suggesting that the efficacy of BI is not restricted to either the early or the late part of the 6-month treatment period, that patients treated with BI engage in treatment early, and that the treatment effect is sustained throughout the 24-week period.

30.2.5.2 Additional Efficacy Measures and Data

Study completion was assessed as a marker of treatment duration. A greater proportion of patients assigned to BI (65 % in PRO-805 and 64 % in PRO-806) compared with PI (28 % and 26 %, respectively) completed the studies. This analysis was prospectively defined and protected in the fixed testing sequence. In addition, a supportive, exploratory survival analysis (Kaplan-Meier) showed that the group difference in time to study discontinuation was nominally statistically significant in both studies ($P < 0.0001$), favoring BI over PI. In the open-label SL buprenorphine arm of PRO-806, the completion rate was 64 %.

Opioid withdrawal symptoms and cravings were assessed by the Subjective Opioid Withdrawal Scale (SOWS) (Dijkstra et al. 2007), the Clinical Opioid Withdrawal Scale (COWS) (Tompkins et al. 2009), and the Opioid Craving Visual Analog Scale (VAS, patient-rated assessment of cravings on a scale of 0 (no craving) to 100-mm (maximum possible)). Mean scores for withdrawal

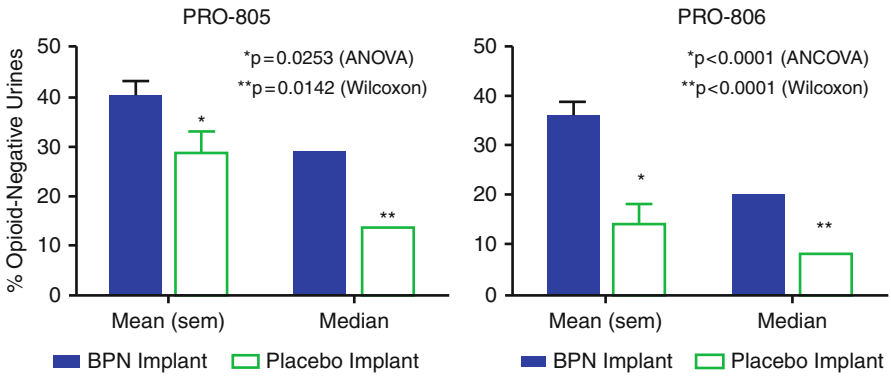

Fig. 30.2 Mean, median percentage of opioid-negative urine samples, weeks 1–24

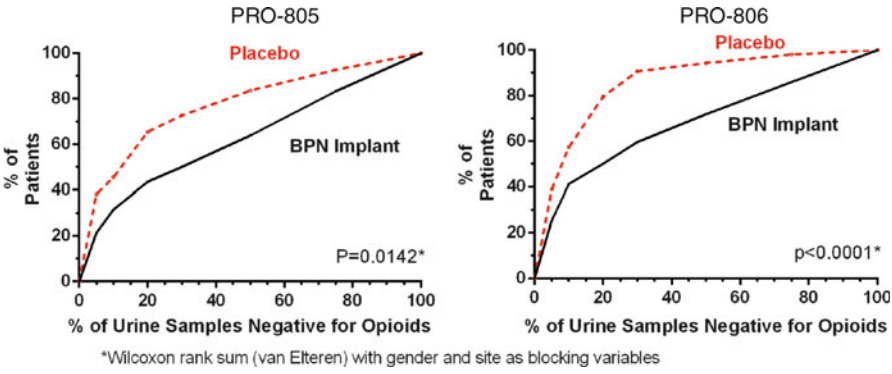

Fig. 30.3 CDF of the percentage of opioid-negative urine samples, weeks 1–24

symptoms and cravings as assessed by these measures were similar in the BI and PI groups at baseline (immediately following SL buprenorphine induction) but were significantly higher (reflecting more withdrawal symptoms and craving) in the PI groups compared to the BI groups ($P < .0001$ for all scores) across 24 weeks of treatment. These results support that opioid withdrawal symptoms and cravings (both self- and observer-assessed) were better controlled, in a clinically and nominally statistically significant sense, in the BI group than in the PI group.

Clinician-rated Clinical Global Impressions-Severity (CGI-S) (of opioid dependence) and Improvement scales (CGI-I) (Guy 1976) were obtained at weeks 16 and 24. At week 16 the proportion of "responder" patients was higher in the BI groups than in the PI groups for both the CGI-self and CGI-observer scores, although the differences were not nominally statistically significant. At week 24, the differences between the two treatment groups had increased and were nominally statistically significant on both scores in study PRO-805 and for

observer-rated status in PRO-806. Overall, the majority of the BI groups was considered responders at study end, while only a minority of the PI groups was self- or observer-rated responders.

Supplemental SL buprenorphine use was allowed by design as rescue medication in the placebo-controlled trials for subjects in all treatment groups when clinically indicated. This allowed for adequate treatment of patients who were not responsive to the starting dose of four BI or were assigned to the PI arms. In the double-blind studies, the majority of patients in the BI group were treated with four implants and did not require a dose increase. More specifically, 63 % of patients who were treated with four BI and 45 % of patients, after receiving a fifth Buprenorphine Implant, took no sublingual rescue medication. In the open-label studies, 79 % of the four BI groups and 67 % of the five BI groups took no supplemental rescue medication. Of 83 patients who completed both double-blind and open-label studies, 41 (or 49 %) took no supplemental rescue medication over two sequential 24-week treatment periods.

Open-label extension studies PRO-807 and PRO-811 supported the efficacy results of the double-blind Placebo Implant-controlled preceding studies. For example, during the second 6-month treatment period, plasma buprenorphine exposure and study completion rates (74.2 % in study PRO-807 and 78.8 % in study PRO-811) were comparable to those achieved in the BI group in the first 6-month treatment period.

30.2.5.3 Exploratory Comparison of Buprenorphine Implants to Active Comparator SL Buprenorphine

Study PRO-806 included an exploratory open-label active comparator arm, in which patients received SL buprenorphine/naloxone (Suboxone®) at doses up to 12–16 mg/day. The protocol pre-specified comparison relevant to the active control was an analysis of the difference in proportions of urine samples negative for illicit opioids from week 1 to week 24 with a pre-specified non-inferiority margin of –15 %. Buprenorphine Implants met the non-inferiority criterion with similar proportions of opioid-negative urine samples in the BI group (31.3 %, $N = 114$) and the SL buprenorphine/naloxone group (33.5 %, $N = 119$) and the lower bound of the 95 % confidence interval for the difference in proportions greater than –15 % (95 % CI –10.7, 6.2). In additional exploratory analysis, the CDFs of the percentage opioid-negative urines over weeks 1–24 in the BI and SL buprenorphine/naloxone groups did not differ significantly. Study completion rates were similar in the BI arms of study PRO-805 (65 %) and PRO-806 (64 %) and the open-label SL buprenorphine/naloxone arm of PRO-806, (64 %). Finally, a post hoc analysis of the proportions of patients with at least 4 weeks of continuous abstinence defined as no positive urine tests (three per week) combined with patient self-reported opioid use showed comparable rates of 4-week abstinence between the BI ($n = 69$) and SL buprenorphine ($n = 119$) groups of 29 % in each group compared to PI ($n = 54$) of 3.7 %. The BI and PI group comparison was performed using a Cochran-Mantel-Haenszel test stratified on gender and pooled site, $p = 0.0002$. This post hoc analysis excluded any BI patient who was treated with rescue SL buprenorphine/naloxone.

30.3 Conclusion

Collectively, the data of six clinical studies indicate that Buprenorphine Implants are a safe and efficacious maintenance treatment for opioid dependence. BI was superior to PI in both double-blind studies for the primary outcome measure, the proportion of urine samples negative for opioids. Secondary and exploratory endpoints supported the conclusion that BI was more efficacious than PI. These included analyses of opioid-negative urines during various segments of the treatment period, the proportion of patients completing each study, measures of opioid withdrawal symptoms and cravings, patient- and observer-rated improvement in opioid dependence, and use of supplemental buprenorphine. In secondary and exploratory comparisons, BI and open-label SL buprenorphine resulted in similar proportions of opioid-negative urine samples over 24 weeks, documenting the overall comparability of 4–5 Buprenorphine Implants to sublingual buprenorphine (12–16 mg/day) in a 6-month treatment for opioid dependence. The Buprenorphine Implants clinical program demonstrated safety and efficacy of Buprenorphine Implants for the maintenance treatment of opioid dependence.

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Use of Different Drug Formulations of Opioid Antagonist (Naltrexone) to Treat Opioid Dependence in Russia

31

Evgeny Krupitsky, Edwin Zvartau, and George Woody

Contents

Abstract

Opioid addiction is one of the most severe drug problems due to its high level of morbidity, mortality, and psychosocial consequences. Naltrexone completely blocks the effects of opioids and, when administered to detoxified opioid addicts and taken as directed, prevents relapse and reduces the chances for a wide range of adverse effects associated with untreated addiction. It has been available as a 50 mg tablet since the mid-1970s, and early studies showed very limited efficacy due to lack of interest by patients, high dropout rates, and a preference for methadone maintenance. In addition, patients must be detoxified and free of physiologic opioid dependence prior to starting naltrexone because it

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will precipitate withdrawal if given to a person who is currently dependent, and such services are not always available or prohibitively expensive. In Russia, the law prohibits use of methadone, buprenorphine, and other opioid agonist therapies, and naltrexone is the only effective pharmacotherapy available for treating opioid addiction. Inpatient detoxification followed by 1–3 months of residential treatment is the standard treatment for opioid addiction. A number of randomized, placebo-controlled trials have been conducted in Russia that have demonstrated efficacy of the oral formulation with younger patients who are living with their families; that combining oral naltrexone with an antidepressant (fluoxetine) or an α-*adrenergic agonist* (guanfacine) does not increase the proportion of patients who remain in treatment without relapsing and that sustained-release formulations (injectable and implantable) are more effective compared with oral formulations and placebo. The implant that has been studied (Prodetoxone®) prevents relapse for 2–3 months and the injectable formulation (Vivitrol®) prevents relapse for a month. This chapter will summarize the results of these studies, all conducted in Russia during the past 13 years.

31.1 Introduction

Naltrexone, an opioid antagonist, was approved by the US Food and Drug Administration to treat opioid dependence in 1984. Approval was based primarily on its pharmacologic profile, as it blocks opioid effects by antagonism at the μ-opioid receptors (Kleber 2007). Naltrexone is a perfect antagonist for treating heroin dependence, as 50 mg (one tablet) blocks the effects of heroin for 24-36 h; it is easy to administer (one tablet per day or two tablets every other day), safe (no common serious adverse events if used in recommended doses), and well tolerated (a relatively small number of side effects) and does not have addictive potential; and tolerance does not develop to the opioid antagonism.

However, one problem markedly reduces naltrexone's efficacy and has limited its use for treating heroin and other forms of opioid dependence worldwide: patients often do not like it and do not take it on a daily basis. The dropout rate with oral naltrexone has been better in the limited number of patients in whom there is substantial external motivation to remain abstinent, such as physicians who are in monitoring programs and could lose their license if they relapse, those involved in the criminal justice system who could go to prison if they relapse, and those facing loss of employment (O'Brien and Cornish 2006; Kleber 2007).

Recent World Health Organization guidelines for the pharmacologic treatment of opioid dependence suggest that the limited evidence available demonstrates that in dependent opioid users who have withdrawn from opioids, those treated with naltrexone are less likely to use heroin or engage in criminal activity than those who do not take naltrexone, but the proportion who continue taking naltrexone has been very low (World Health Organization 2009). However, our recent studies of naltrexone for treating opioid dependence in St. Petersburg, Russia, have shown that in some cultural settings, naltrexone may be much more effective. In particular,

Russian law forbids substitution therapy for opioid dependence with methadone or buprenorphine, and the national health-care system supports over 25,000 inpatient detoxification and rehabilitation treatment beds, thus making it easy to start patients on naltrexone. Naltrexone is the only specific pharmacotherapy that is currently approved for use in the Russian Federation and is available as an oral tablet and two extended-release formulations: implantable and injectable. The results of studies using these formulations are summarized below.

31.2 Naltrexone Studies - Russian Context

31.2.1 Studies of Oral Naltrexone

31.2.1.1 Naltrexone Only

Our first relatively small ($n = 52$ patients), double-blind, placebo-controlled, randomized trial of naltrexone for opioid dependence began in the late 1990s (Krupitsky et al. 2004). At that time, Russia faced a dual epidemic of HIV and heroin addiction that had been spreading rapidly. Treatment of opioid dependence consisted of detoxification and drug-free rehabilitation, but relapse rates were high. We hypothesized that naltrexone may be an effective treatment in Russia for several reasons: (1) heroin addicts are mostly young people living with their parents, who are usually the initiators of treatment and can control the daily process of taking naltrexone; (2) heroin addiction is generally not accompanied by use of other drugs; and (3) use of agonists for addiction treatment is illegal, thus naltrexone is the only pharmacotherapy available for treating this disorder. That pilot study evaluated the efficacy of naltrexone for preventing relapse to heroin addiction in a Russian cultural setting. A total of 52 heroin addicts who completed detoxification at addiction treatment hospitals in St. Petersburg and provided informed consent (mean age, 22 years; dependent on heroin for 2.5 years on average) were randomly assigned to a double-blind, 6-month course of biweekly manualized drug counseling and oral naltrexone, 50 mg/day, or counseling and identical-looking placebo. A close family member (e.g., mother, spouse) agreed to supervise daily dosing. Drug testing and brief evaluations were done at each biweekly visit. Medication compliance was evaluated using a riboflavin marker; more extensive psychometric evaluations were done at 3–6 months. A total of 81 patients were asked if they would be interested in participating: 62 gave informed consent and 52 met study entrance criteria and were randomly assigned. Significant differences in retention and relapse favoring naltrexone were seen beginning at 1 month and continuing throughout the study. At the end of 6 months, 12 of the 27 naltrexone patients (44.4 %) remained in the study and had not relapsed, compared with four of 25 placebo patients (16 %; ($P < 0.05$). Among patients who remained in the study, compliance with medication measured by riboflavin in the urine was high (85–95 %), probably a result of the family involvement. Reductions in HIV risk, alcohol use, anxiety, depression, and anhedonia and improvement in overall function were substantial and about equal in both groups among those who were

retained in treatment. However, the proportion of those retained in treatment was significantly higher in the naltrexone group. Thus, the study demonstrated that cultural factors unique to Russia are associated with greater interest and compliance with naltrexone than in the United States and that oral naltrexone was significantly more effective than detoxification and counseling alone.

Thus, although our first study showed a clear advantage for naltrexone, the number of patients was relatively small, dropout continued to be a problem, and naltrexone did not reduce protracted withdrawal-related psychiatric symptoms. Because an earlier study showed that a selective serotonin reuptake inhibitor (SSRI; citalopram) reduced anxiety, depression, and other protracted withdrawal-related symptoms but did not prevent relapse (Krupitsky et al. 2002), we hypothesized that combining naltrexone with an SSRI might be additive, with the antidepressant alleviating protracted withdrawal-related symptoms and improving adherence to naltrexone and treatment outcome.

31.2.1.2 Naltrexone in Combination with Other Psychoactive Medications

Naltrexone and a Selective Serotonin Reuptake Inhibitor

Although our first double-blind pilot study demonstrated that naltrexone was more effective than placebo for relapse prevention in heroin addicts in Russia, it provided no data to indicate that naltrexone itself reduced the depression, anxiety, and anhedonia that are typically associated with heroin dependence and withdrawal following detoxification. It is possible that psychiatric symptoms increase the risk for dropout and relapse, and, therefore, antidepressants might alleviate these symptoms and thus improve results of naltrexone therapy. Our next study aimed to test this hypothesis using fluoxetine with and without naltrexone (Krupitsky et al. 2006). We chose fluoxetine, as it is approved for use in Russia and was offered at reduced cost by Gideon Richter (Budapest, Hungary). This second study was much larger: 280 heroin addicts who completed detoxification at addiction treatment hospitals in St. Petersburg and provided informed consent were included in a 6-month course of biweekly drug counseling and randomly assigned under double-dummy and double-blind conditions to one of four medication groups of 70 participants each: naltrexone (N, 50 mg daily) plus fluoxetine (F, 20 mg daily), naltrexone plus fluoxetine placebo (FP), naltrexone placebo (NP) plus fluoxetine, or naltrexone placebo plus fluoxetine placebo. The primary outcome was relapse to opioid (heroin) dependence. Urine drug testing and brief psychiatric evaluations were conducted at each biweekly visit, and medication compliance was evaluated biweekly using a riboflavin marker; more extensive psychiatric evaluations were done at 3 and 6 months. Results showed that 414 patients were asked if they would be interested in participating, 343 agreed, and 280 met study entrance criteria and were randomly assigned. At the end of 6 months, 43 % of participants in the N plus F group remained in the study and had not relapsed, as compared with 36 % in the N plus FP group, 21 % in the NP plus F group, and 10 % in the NP plus FP group. Based on the survival analysis and retention rate in 6 months, N plus F and N plus FP were more effective than NP plus FP ($P < 0.001$) and NP plus F ($P < 0.01$).

Fluoxetine (NP + F) did not differ significantly from NP plus FP, and N plus F did not differ from naltrexone alone (N + FP; $P = 0.2$). However, women in the N plus F group showed a trend toward an advantage when compared with women receiving naltrexone and fluoxetine placebo (N + FP; $P = 0.08$), probably due to a higher level of depression, anxiety, and anhedonia in women at study intake compared with men. Thus, it was confirmed in this larger study that naltrexone was more effective than placebo for relapse prevention in opioid addicts in Russia. In addition, naltrexone and fluoxetine, or naltrexone alone, were both more effective than fluoxetine alone, although the combination of naltrexone and fluoxetine had a tendency to be more effective than naltrexone alone in women (Krupitsky et al. 2006). Overall, the antidepressant did not dramatically improve the naltrexone treatment outcome. It should be added that oral naltrexone was generally well tolerated, the number of side effects was limited, and neither serious adverse events nor lethal overdose occurred.

Naltrexone and Presynaptic, α-Adrenergic Agonists

A small pilot study of opioid-dependent patients ($n = 18$) found that a combination of naltrexone and lofexidine (a presynaptic α-adrenergic agonist that has antihypertensive and stress protective properties and reduces opioid withdrawal) may improve naltrexone outcome (Sinha et al. 2007). Lofexidine is used commonly in the United Kingdom for treatment of hypertension and opioid withdrawal and has been studied in the United States to treat opioid withdrawal but is not FDA approved for this indication. A small pilot study by Sinha and colleagues (2007) at Yale University School of Medicine suggested that lofexidine may enhance success rates among patients taking maintenance naltrexone and help them avoid relapse to opioids. However, these results were very preliminary because of the small sample size.

We recently completed a large ($n = 301$ opioid-dependent patients), randomized, double-blind, double-dummy, placebo-controlled, four-cell study of naltrexone and guanfacine (another presynaptic α-adrenergic ligand used to treat hypertension) in collaboration with Dr. T. Kosten of Baylor College of Medicine. Three hundred and one opioid-dependent patients met inclusion criteria, gave informed consent, and were randomized (mean age ± SD = 28.3 ± 4.4 – older than in our previous naltrexone trials) into four treatment groups: naltrexone (N) 50 mg/day + guanfacine (G) 1 mg/day (N/G) ($n = 75$), naltrexone (50 mg/day) + guanfacine placebo (N/GP) ($n = 76$), naltrexone placebo + guanfacine (1 mg/day) (NP/G) ($n = 75$), and double placebo (NP/GP) ($n = 75$). All patients received drug counseling with parental or significant other involvement to encourage adherence. At 6 months (end of treatment) retention in N/G group was 26.7 %, in N/GP group 19.7 % ($p = 0.258$ to N/G), in NP/G group 6.7 % ($p < 0.05$ to both naltrexone groups, Fisher exact test), and in NP/GP 10.7 % ($p = 0.013$ to N + G group, Fisher exact test). Overall, adding guanfacine to naltrexone did not improve outcomes significantly (retention in treatment and number of opioid-free urines). During the 6-month treatment period, HIV risk, depression, anxiety, anhedonia, and craving for opioids gradually reduced among all patients who remained

in treatment and did not relapse, regardless of group assignment; however, guanfacine reduced severity of stress. The frequency of adverse events (AE) was low (4.7 %) with no significant differences between the groups; most common AEs were headache, poor appetite, insomnia, and dizziness.

In summary, combining naltrexone with fluoxetine (an SSRI) or an α-adrenergic agonist has not demonstrated a significant improvement in treatment outcome (with the opioid addicts getting older, the efficacy of oral naltrexone slightly decreased), and we have decided to change the direction of our naltrexone research and study long-acting, sustained-release formulations, as they may improve the adherence problem.

31.2.2 Studies with Long-Acting, Sustained-Release Formulations

31.2.2.1 Implantable Naltrexone

The first long-acting, sustained-release naltrexone formulation available in Russia was an implant (Prodetoxone®; Fidelity Capital, Moscow, Russia). It contains 1,000 mg of naltrexone that is slowly released after being inserted subcutaneously in the abdominal wall via a small incision. It was registered in Russia in 2005 and shown to block opioids for 2 months, but this time frame was extended to 3 months during the past year, based on clinical experience. As of this writing, it is the only officially registered naltrexone implant in the world, and we recently completed a double-blind, double-dummy, placebo-controlled, randomized study of this naltrexone formulation (Krupitsky et al. 2012). In this study, 306 recently detoxified opioid addicts were randomized to a 6-month course of biweekly drug counseling and one of three medication groups (102 patients in each one): naltrexone implant (1,000 mg, three times – every other month) + oral placebo daily (NI+OP), placebo implant + oral naltrexone (PI+ON) (50 mg/day), and double placebo (implant and oral) (PI+OP). Medications were administered under double-dummy/double-blind conditions. Urine drug testing and brief psychiatric evaluations were done at each biweekly visit. Oral medication compliance was evaluated using a urine riboflavin marker. By month 6 (end of treatment), 54/102 (53 %) of NI+OP patients remained in treatment without relapsing compared to 16/102 (16 %) in PI+ON (survival analysis, log rank test $p < 0.001$) and 11/102 (11 %) in PI+OP ($p < 0.001$). The PI+ON vs. PI+OP comparison showed a nonsignificant trend favoring PI+ON ($p = 0.069$) but was significant ($p < 0.024$) when limited to those with proven relapse. Counting missing tests positive, the proportion of opiate negative urines was 63.6 % (CI: 60–66 %) for NI+OP, 42.7 % (CI: 40–45 %) for PI+ON, and 34.1 % (CI: 32–37 %) for PI+OP ($p < 0.0001$, Fisher exact test to NI+OP group). There were 12 wound infections among 244 implantations (5 %) in the NI+OP group, two among 181 implantations (1 %) in PI+ON, and one among 148 implantations (1 %) in PI+OP ($p < 0.01$, Fisher exact test). All were in the first 2 weeks after implantation and resolved with antibiotic treatment. There were four local site reactions (redness and swelling), all in the 2nd month after implantation in the NI+OP group ($p = 0.12$, Fisher exact test); all resolved with anti-allergy medication.

Using the number of visits as the denominator, nonlocal site AEs were reported by 8/886 (1 %) in the NI+OP group, 4/522 (1 %) in the PI+ON group, and 3/394 (1 %) in the PI+ON group; none were serious and all resolved without medication. There was no evidence of increased overdose death after naltrexone treatment ended. Thus, the implant was more effective than ON or placebo. More patients in NI+OP than in the other groups developed wound infections or local irritation at the implant site, but none were serious and all resolved with treatment (Krupitsky et al. 2012).

No significant differences were detected between groups in physical and social anhedonia, thus implying that the long-acting naltrexone did not interfere with normal pleasurable stimuli. Similar to our studies with oral naltrexone, psychiatric symptoms (anxiety, depression, opioid craving) were markedly reduced in patients who remained in treatment and did not relapse, and no differences were noted between groups for those who remained in treatment and did not relapse. The efficacy of oral naltrexone was lower in this implant study compared with our previous oral naltrexone studies (Krupitsky et al. 2004, 2006), which may be related to the age of opioid addicts and the degree to which family members could supervise compliance. For example, the mean age of patients in the implant study was 28-29 years, significantly higher than previous studies, in which the average was 21-23 years. These older patients were less likely to be living with relatives, which made it more difficult for the relatives to supervise compliance.

Results of two recent randomized trials of another naltrexone implant developed in Australia also demonstrated its advantages over oral naltrexone (Hulse et al. 2009) and usual-treatment aftercare (Kunoe et al. 2009); however, these studies did not have a placebo control group. Other long-acting, slow-release naltrexone formulations (implantable and injectable) for opioid dependence are being developed and tested (Krupitsky and Blokhina 2010).

Implantable naltrexone formulations have several limitations. First, they require a minor surgical procedure that carries with it the risk of wound infections and cosmetic defects. Second, it is possible for the patient to remove the implant within the first few weeks, as Prodetoxone slowly dissolves and can be removed reasonably intact within the first few weeks. Third, in some patients (<10 %), the implant appeared to block opioids for less than 2 months. Therefore, a long-acting, slow-release formulation that is injectable and simple to use and does not require surgery might have some advantages over an implant formulation.

31.2.2.2 Injectable Naltrexone

Three sustained-release, injectable naltrexone formulations have been developed in the past 10-15 years: Vivitrol® (Alkermes, Waltham, MA), Depotrex® (Biotech, Bethesda, MD), and Naltrel® (Drug Abuse Sciences, Hayward, CA). Only Vivitrol® has US Food and Drug Administration approval. It is administered via a monthly intramuscular injection and blocks the subjective effects of opioids for 1 month (Dunbar et al. 2007).

The effectiveness of Vivitrol® for preventing relapse to opioid dependence was recently studied in a phase 3, double-blind, placebo-controlled, randomized,

multicenter trial (Krupitsky et al. 2011). The study, conducted at 13 sites in Russia, recruited males and females (≥18 years) meeting DSM-IV criteria for opioid dependence disorder, who had completed inpatient opioid detoxification (≤30 days) and who were off opioids for ≥7 days. Patients were voluntarily seeking treatment and were excluded if they were under justice system coercion, i.e., parole or probation, or pending legal proceedings with potential for incarceration. Patients were randomized to either injectable naltrexone 380 mg (Vivitrol®) or placebo in a 1:1 ratio, stratifying by site and gender in a centralized, permuted-block method. Vivitrol® was injected within 1 week following detoxification and then every 4 weeks, for a total of six injections over 24 weeks. Participants were also offered 12 biweekly sessions of manualized individual drug counseling (IDC), adapted for opioid dependence. The primary outcome was the response profile for confirmed abstinence, based on opioid-negative urine drug tests and self-report of nonuse during weeks 5–24. Patients were predominantly young, male, white, and addicted to heroin for ~10 years and had high rates of HIV and hepatitis C infection. In the 30 days prior to the first injection, heroin was used by 221 (88.4 %) of participants, methadone by 29 (11.6 %), and other opioids/analgesics by 33 (13.2 %). Baseline characteristics showed no significant intergroup differences. Vivitrol® yielded a median of 90 % confirmed abstinent weeks vs. 35 % for placebo ($p = 0.0002$); total abstinence occurred in 36 % of Vivitrol® patients vs. 23 % ($p = 0.0224$). An anti-craving effect was observed; at baseline (scale 0–100), there was no group difference (21.8 vs. 18.2); however, during treatment Vivitrol® showed a mean reduction of −10.1 (vs. +0.7 for placebo; $p < 0.0001$). Median retention was >168 days with Vivitrol® vs. 96 days with placebo ($p = 0.0042$). Naloxone challenge confirmed relapse to physiologic opioid dependence in 17 placebo patients vs. one Vivitrol® patient, a 94 % difference ($p < 0.0001$). Reduced HIV risk behavior and improved mental health function were observed with Vivitrol® vs. placebo. Adverse events were reported by 50 % on Vivitrol® vs. 32.3 % on placebo. Mean increases, for Vivitrol® vs. placebo, were similar for ALT (6.9 vs. 5.6 IU/L) and AST (3.8 vs. 6.7 IU/L), but hepatic enzyme abnormalities were more common with Vivitrol®. All nonserious adverse events were rated mild or moderate and included nasopharyngitis, insomnia, injection site pain, and toothache. No patients died or overdosed. Thus, in opioid-dependent patients, Vivitrol® with counseling demonstrated efficacy vs. placebo across multiple recovery goals including prevention of relapse, showing that it represents a new approach that is distinct from opioid maintenance treatment through once-monthly, injectable, opioid blockade.

31.3 Conclusion

Studies conducted in St. Petersburg, Russia, for more than a decade have demonstrated the efficacy and safety of different naltrexone formulations (oral, implantable, injectable) for relapse prevention and maintenance of abstinence in detoxified opioid addicts. The positive results from different formulations seem related to two

cultural factors. One is that detoxification is widely available and relatives can be recruited to supervise daily dosing of the oral formulation; however, this advantage appears to decrease as the population ages. The second is that substitution therapy is not available; thus, naltrexone is the only effective medication, which makes it easier to motivate patients to use it. Findings from studies of long-acting, extended-release formulations (implantable and injectable) show that they are more effective than oral formulations and likely to be important additions to current treatment options not only in Russia but also for patients in other settings who do not want or do not have ready access to agonist or long-term residential treatment. How extended-release naltrexone formulations compare with maintenance treatment using methadone or buprenorphine in settings in which all three treatment options are available is a topic for future studies.

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Implementation of Methadone Maintenance Treatment in China

32

The Response to HIV/AIDS Epidemics Among Drug Users

Min Zhao

Contents

Abstract

China has a long history of opium abuse problems and currently faces the challenge of a dual epidemic of drug use and HIV/AIDS. China has adopted methadone maintenance therapy (MMT) as a primary strategy to combat this dual epidemic. The results from the studies have shown that most of the interventions MMT programs were successful and had positive effects in reducing drug-related risk behaviors among drug users. It is expected that the

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coverage and quality of the MMT programs will improve and they will fully achieve their goals in the near future.

32.1 Introduction

China is the largest populated country in the world and suffered from a long history of opium abuse problems. As for economic development and modern socialization, like other Western countries, China faces the challenge of dual epidemics of drug use and HIV/AIDS. The former has fuelled the latter and in the last 30 years, both the number of drug users and cases of HIV/AIDS have increased dramatically. This has prompted the government to consider employing harm reduction strategies to control the spread of HIV/AIDS among drug users. Following the success of the proven "substitution" pharmacotherapy approach that has been tested extensively in the Western nations, China has adopted methadone maintenance therapy (MMT) as a primary strategy to combat the combination threat of drug use and HIV/AIDS. MMT program has been implemented in China for nearly 10 years and achieved remarkable progress with the support of central government.

32.2 The Epidemic of Drug Use and HIV/AIDS in China

China has had a long history of drug use, especially opium abuse. The country enjoyed a relatively drug-free period between the 1950s and 1980s due to a successful antidrug campaign. Shortly after the new Chinese government established in 1949, under Mao's leadership, the government launched a national level antidrug campaign, which included compulsory detoxification of drug abusers, severe punishment for drug dealers, and the replacement of opium with other crops, and was greatly assisted by closing the borders (McCoy et al. 2001). However, in the late 1970s, China introduced its "open door" and economic development policy. China is close to the "Golden Triangle" and "Golden Crescent," two of the three biggest opiate suppler areas in the world. Concurrent with increased trade of licit goods, the trade in illicit goods, including narcotics, reemerged (Zhao et al. 2004). When drug use reemerged in the late 1970s, it was concentrated in Yunnan and Guangxi provinces which border with Myanmar and Vietnam. At that time, Chinese authorities were under the impression that China only served as a trafficking route for drug smugglers to traffic drugs to other countries and that there was no or little drug consumption. Efforts were exclusively focused on seizures of smuggled drugs, with little attention given to prevention and treatment of drug use among the Chinese. Along drug traffic routes, more and more youths and young adults became drug users, and later, drug use spread very quickly from border areas to inner regions of the country (Zhao et al. 2004). It was not until the mid-1990s that Chinese officials and scholars recognized that drug use was a severe social problem. China's Public Security Bureaus (PSB) started to register drug users in 1990. The registered number of drug users in 1990 was 70,000 and this

figure rose to 1.79 million in 2011 (National Narcotic Control Commission 2012), representing a rapid epidemic of drug use problems in China.

With the drug use problem increasing rapidly, the drug use-related family, social, and public health problems become more and more oblivious. One of the severe public health consequences is HIV/AIDS transmission among drug users. Needle sharing to inject heroin is believed to have been the principal entry route of HIV into China. Indeed, first HIV outbreak was identified among 146 injecting drug users in Yunnan province in 1989 (Wang 2007). Since then, China has observed an ever-growing HIV/AIDS epidemic. In 2001, up to 66.5 % of newly diagnosed HIV infections were related to drug use. The prevalence of HIV is highest in those provinces located closest to the borders of Myanmar (Yunnan Province), Vietnam (Guangxi Autonomous Region), and Central Asia (Xinjiang Uygur Autonomous Region). The HIV/AIDS has spread rapidly through the injecting drug user (IDU) population and had reached IDUs in all 31 provinces by 2002. By the end of 2005, HIV was estimated to have infected 288,000 drug users, accounting for 44.3 % of China's 650,000 HIV infections (Bao and Liu 2009). The prevalence of HIV in China is roughly 0.05 %, but among drug users it is much higher and surveys among drug users have found the prevalence to be 12.5 % among drug users (Bao and Liu 2009). Facing the threats of HIV/AIDS epidemics among drug users, harm reduction efforts began in 2003 and have slowed the pace of HIV infection among drug users has stabilized and reduced, particularly since 2005, with the overall growth rate of newly reported cases having decreased from 9.0 % in 2006 to 5.8 % in 2009. By the end of Oct. 2012, 492,000 HIV-infected cases were reported and 25.8 % of the cases were injecting drug users (IDUs). It was thought that IDU is no longer the major HIV/AIDS transmission mode in China. Among the harm reduction strategies, methadone maintenance treatment was the most successfully implemented program in China.

32.3 The Development of Methadone Maintenance Treatment Program

In the early 1990s, government officials began the lengthy process of understanding how best to constrain the dual epidemic of HIV and drug use. This included learning from other countries, developing policies and plans suitable to China, piloting harm reduction strategies, and ultimately implementing a multifaceted program to slow the HIV epidemic among drug users. When first introduced, harm reduction was controversial because it conflicted with laws and regulations on narcotics control. Thus, despite a large body of evidence supporting the effectiveness of MMT, it was initially difficult to convince government officials, especially those in law enforcement, to try this strategy (Yin et al. 2010). But finally the National Center of AIDS/STD Control and Prevention (NCAIDS) make great effort to develop MMT program as a strategy to control HIV transmission by several phases.

32.3.1 Preparation Phase

In order to advocate for implementation of MMT program to control HIV/AIDS epidemics, public health professionals from the National Center of AIDS/STD Control and Prevention (NCAIDS) took the bold step to explore the feasibility and effectiveness of MMT by conducting pilot interventions to advocate for evidence-based policy. Prior to 2001, efforts focused on policy advocacy and preparation. The Medium-and Long-Term Strategic Plan for HIV/AIDS (1998–2010) issued in 1998 was China's first HIV-specific policy document with clear targets. It resolved to contain the rapid spread of HIV among injecting drug users and mandated HIV/STD education in drug rehabilitation centers and prisons, as well as in schools. Thus, harm reduction as a control strategy was formally introduced (Li et al. 2010). The plan called for a pilot of Maintenance Treatment for Opiate Users in therapeutic institutions. The National Working Group for Community-based Maintenance Treatment for Opiate Users (hereafter referred to as the National Working Group) was established in August 2002, consisting of members of the Ministries of Health, Public Security, and the State Food and Drug Administration and experts on addiction and HIV/AIDS. The national guidelines were drafted by the secretariat and reviewed by National Working Group members, and further consultation was sought from stakeholders (Wu et al. 2007). In February 2003, the Ministry of Health, the Ministry of Public Security, and the State Food and Drug Administration jointly issued the Temporary Scheme for Community-Based Drug Maintenance Treatment for Heroin Dependents.

32.3.2 The Pilot Phase

The temporary scheme prioritized MMT implementation in those areas most severely affected (more than 500 drug users) and outlined eligibility criteria for participation. The eligibility criteria to participate in MMT were (1) opiate users who had failed more than one attempt to quit, (2) at least two terms in a detoxification center or once in a reeducation-through-labor detoxification facility, (3) at least 20 years of age, (4) a local resident and settled in the local area where the clinic was located, and (5) capable of complete civil liability. Drug users testing HIV positive needed only to fulfill requirements (4) and (5) to qualify. The temporary scheme also outlined the safety and security protocol to guide methadone production, transport, and distribution under the supervision of the State Food and Drug Administration. Methadone powder was purchased centrally and distributed to participating provinces, which have each assigned one pharmaceutical body to produce methadone liquid according to the Chinese pharmacopoeia. In addition, it was stipulated that the maximum daily cost for a drug user receiving MMT services is 10 Chinese Yuan per day (US $1.20) irrespective of dosage. Patients had to appear in person to collect their daily dose. Between March and June 2004, the first eight MMT clinics were established: two in Sichuan, one in Yunnan, two in Guizhou, one in Guangxi, and two in Zhejiang (Wu et al. 2007). The locations of

the clinics were based on need and the local government agencies' willingness to participate. A total of 1,029 clients were enrolled during the first calendar year of the pilot. To estimate the effectiveness of these first eight clinics, the national secretariat established a monitoring and evaluation system.

32.3.3 The Scale-Up Stage

In 2004, the first national meeting on piloting MMT was convened among experts and government officials from Ministry of Health and National Narcotics Bureau. The meeting served to share the experiences and to promote rapid scale-up throughout the country. With growing political and technical support, the MMT program began to steadily expand. By the end of 2005, there were 58 MMT clinics opened in 11 provinces. Thus, the pilot period ended and the MMT program moved to national scale. In 2006, the adjoining Five-Year Action Plan to Control HIV/AIDS (2006–2010) set specific targets for scaling up MMT; by the end of 2007 and 2010, MMT would be made available for no fewer than 40 % and 70 % of opiate users, respectively, in counties and districts with more than 500 registered drug users (State Council of P. R. China 2006). Also, in July 2006, the National Working Group revised the temporary scheme to improve MMT services. Several crucial improvements were made to benefit and cover more target groups. Notably, the enrolment and exclusion criteria were relaxed. For example, (1) clients are no longer required to have a history of detoxification or several failed attempts to quit using drugs to enter the program, (2) clients are no longer required to be registered as local residents and a transfer system has been set up to meet the needs of those who are relocating either permanently or temporarily, and (3) relapse is no longer a strong reason for expulsion. Furthermore, a detailed clinical guideline for methadone treatment was added to the protocol to support clinical practice, and comprehensive interventions are highlighted in the new protocol that suggests clinics offer ancillary services. These include counseling, psychosocial support, testing for HIV, syphilis, hepatitis C and tuberculosis, referrals for antiretroviral treatment, peer education, health education, group activities, and skills training for employment. The treatment fee for MMT services was not specified, as in some areas where heroin is easily obtained at low cost, the fee is reduced or even waived. In 2007, central government funding was also allocated to the program, enabling those places with less than 500 registered drug users to establish MMT clinics. Another target of 500 MMT clinics was set and 503 MMT clinics were cumulatively accomplished by the end of 2007, in 23 provinces serving 97,554 clients.

32.3.4 The Quality Improving Phase

There were 680 clinics by the end of 2009, in 27 provinces with some 242,000 clients ever enrolled, roughly half of whom remain in treatment. Areas of greatest need have MMT clinics and the expansion has thus slowed down and then the focus

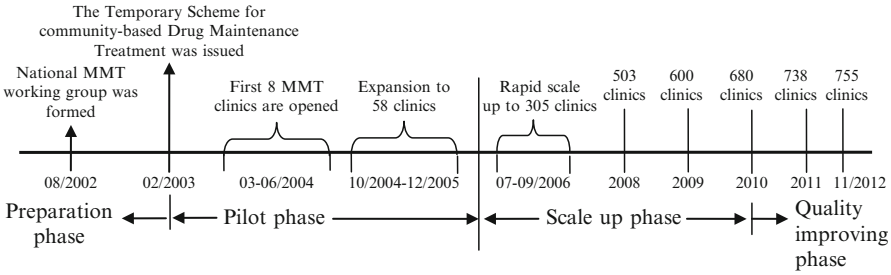

Fig. 32.1 The development process of MMT program in China

of the National Working Group is focused on improving the service quality. It was emphasized to improve the retention rates and a series of intensive training was carried out to improve the service quality. Clinic services have been extended to offer clients a range of ancillary services, including HIV, syphilis, and hepatitis C testing; information, education, and communication; psychosocial support services; and referrals for treatment of HIV, tuberculosis, and sexually transmitted diseases. Regular evaluation and professional supervise were organized to identify problems and provide technical support. By the end of Nov. 2012, there were 755 clinics in 28 provinces with 381,900 clients ever enrolled, roughly 78.2 % of whom remain in treatment within 1 year. The development process of MMT program in China is illustrated in Fig. 32.1.

32.3.5 MMT Mobile Service

China is a vast country with many rural areas where the density of population is varied largely. In order to provide MMT services to drug users in remote, rural areas to access to methadone, the first MMT mobile service vehicle was established in Nov. 2006 in Yunnan province. The mobile MMT service vehicle serves as a small MMT clinic, equipped with necessary medical equipment, medicine, and qualified professionals and securities. Every day the mobile MMT service vehicle travels decades of miles with several fix stops where the patients are concentrated. Following the success experiences in Yunnan, the mobile services were available later in other provinces, with a total of 30 MMT vehicles by the end of Nov. 2012.

32.3.6 Extension MMT Service Site

In recent 2 years, in order to improve the accessibility and service coverage of MMT, it was encouraged to set up MMT extension service site based on the existing MMT clinics (fixed MMT clinics) in the area. The extension MMT service site can be established in countryside or community health service center where patients are relatively concentrated resided but no fixed MMT clinics available. The fixed MMT

clinics are responsible for the technique support such as staff training and clinical supervision for the extension sites. The fixed MMT clinics are also in charge of the everyday clinical management such as patients recruit, data collection, laboratory test, and methadone delivery in the extension MMT service sites. There are 308 extension MMT service sites available by the end of November 2012 since it was first opened in Yunnan province.

32.4 The Governance and Technical Support for MMT

The National Working Group was given an overall responsibility for managing the MMT program, supervising the operation, and overseeing its expansion. At the provincial and county level, working groups have also been established to take on these duties locally. The National Working Group members meet regularly to identify potential gaps, resolve emerging issues, and refine the management of the program. The NCAIDS serves as the secretariat for the National Working Group, which is tasked with executing the national plan, coordinating the implementation, providing technical support to the clinics, and conducting routine monitoring and evaluation. The national training center was established in the Yunnan Institute of Drug Abuse to provide clinical and administrative training for key staff working in MMT clinics. Two specific training programs are provided to trainees. The first is a 10-day intensive training course covering addiction theory, clinical practice, and administrative skills for delivery of MMT services. The second is on-site training provided by clinical addiction experts to assist local staff for the first 7 days after a clinic has opened, to guide them in the practice of addiction treatment and data management. The MMT clinics in China are nonprofit medical facilities assigned by local public security and public health departments to be established and operated by local Centers for Disease Control and Prevention (CDC), primary health hospitals, mental health hospitals, or voluntary detoxification centers in areas with a concentration of drug users. Typically, an MMT clinic is required to have eight to ten staff members including qualified doctors, pharmacist, security personnel, etc. Doctors are primarily responsible for prescribing methadone, providing physical examination, and psychological counseling, and they are required to be certified physicians authorized to prescribe analgesic and psychotropic drugs. Nurses are responsible for dispensing methadone to the clients and observing them taking the methadone. Other clinic staff members are responsible for data entry, management, report, and other logistical issues. One or two security personnel are required for each of the MMT clinic. Patients meet with the doctor every day and pay not more than 10 Yuan (or US $1.25) for the daily dosage. Urine testing is routinely required. The services offered at methadone clinics have been broadened and provide access to other services, including HIV and hepatitis testing, antiretroviral therapy for eligible AIDS patients, group activities, peer education, and skills training for employment. Regular monitoring and evaluation need to be carried out to quality control. A national MMT program database was developed in 2004 to monitor the pilot and was later upgraded to a web-based management

database in 2008. The database enables regular reporting on the implementation of the program. Such information can be used to identify gaps in the delivery of services in a timely manner. Each of the clinics uploads its daily services records to the database in real time. This includes clients' demographic information at the start of treatment, as well as their daily dose record and the results of any tests performed for opiate use, HIV, hepatitis C, syphilis, and tuberculosis. The information is collected at entry, 6 months after entry, and 12 months after and then at 12-month intervals thereafter, allowing the secretariat to measure the relative change in clients staying in the program in order to evaluate the effectives of MMT.

32.5 The Outcomes of MMT Programs in China

The results of the empirical studies in China revealed that most of the interventions of MMT program were successful and had positive effects in reducing drug-related risk behaviors among drug users. A 2007 evaluation survey conducted in the first phase of eight MMT clinics found a positive change in the self-reported rate of injecting drug use, drug-related illegal offenses, employment opportunities, and family relations. Only eight HIV seroconversions were found among 1,153 sero-negative clients during the 12-month follow-up (Pang et al. 2007). Another two MMT intervention studies showed that the use of MMT decreased the frequency of IDU and criminal behaviors. The sentinel surveillance data showed that HIV infection prevalence among drug users has been leveled off and has a tendency to decrease after the MMT program was implemented in China (Yin et al. 2010, Fig. 32.2).

These positive results are consistent with the large body of empirical evidence on effectiveness of harm reduction programs in other countries. One study in Yunnan province analyzed the cost and cost-effectiveness of methadone maintenance treatment (MMT) program, and it demonstrates that MMT is a cost-effective

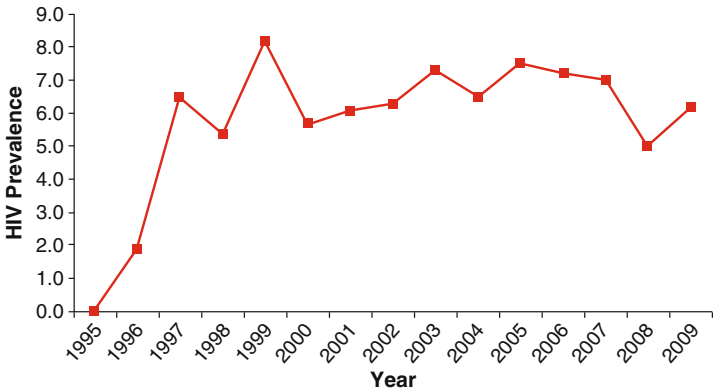

Fig. 32.2 HIV sentinel surveillance data for drug users, 1995–2009

intervention for reducing HIV transmission among injecting drug users (Xing et al. 2012). In summary, the MMT program not only decreased the drug use and HIV transmission; it was also a cost-effective intervention.

32.6 Challenges and Future Direction in MMT

China has made substantial progress in the development and implementation of MMT programs and many positive outcomes from the program have been shown within just less than 10 years since it started in 2004. However, program planners, researchers, and policy makers of MMT programs are facing several special challenges that need to be addressed in future (Lin et al. 2010).

32.6.1 The Service Coverage and Utilization Needs to Be Increased

First, despite a high number of registered opiate addicts in the country, the number of clients in the MMT program is very limited, with low coverage of the total drug-using population (Li et al. 2007). There is great variation in the numbers of clients in each MMT clinic, some with more than 200, whereas others have fewer than 20. According to the newest data from the National Working Group's report recently, there are 755 MMT clinics, and only 209,400 clients (less than 20 % of the registered number of drug users) are currently in the treatment. The majority (63.8 %) of the MMT clinics only had less than 200 clients. Clearly the program does not reach the majority of opiate addicts, although there is adequate capacity to handle more clients.

Given human resources constraints and the size of the country, it is not feasible to offer MMT services in all areas with drug use. It is pragmatic to provide the service in the worst affected areas first, and only areas with more than 500 drug addicts had MMT clinics. The denominator used to calculate the targeted clients is currently registered drug users, which may be significantly less than the actual number. Although mobile MMT service vehicles and extension MMT service site have been implemented to increase the service coverage in some areas, it may be a long time before services are more widely accessible. The existing MMT clinics can serve much more clients than the actual number of clients in MMT programs now; therefore, a very important strategy should focus on how to increase the service utilization. In-depth research are needed to find out the barriers for service utilization, and related adjustment on policy and operation of the MMT programs should be taken to address these barriers.

32.6.2 The Retention of the Clients Need to Be Increased

Second, the client dropout rate is high in most sites (Qian et al. 2006) and a considerable proportion of clients continue illicit drug use while participating in MMT.

The MMT program has suffered from a high relapse rate, especially in its initial phases. In 2009, the overall retention of MMT in China was about 50 % and most of the clients who dropped out relapsed to drug use.

Previous studies have documented that both treatment and individual level characteristics are associated with treatment retention. Treatment characteristics are crucial predictors of retention and drug use. For example, methadone dosage is strongly positively associated with retention and other favorable treatment outcomes. MMT clients in China receive lower dosages of methadone compared with patients treated in other countries. The average daily dosage of methadone given to Chinese clients in eight pilot MMT clinics was 44.9 ± 21.9 mg (Pang et al. 2007). One qualitative study showed that the average dosage prescribed in the 28 clinics was 35 mg per day (Lin and Detels 2011). Therefore, it is necessary to formulate clear guidelines concerning individualized dosage management and to improve training among service providers in MMT clinics in China. The National Working Group has realized the abovementioned problems and challenges and is making a great effort to solve these problems. The scale-up pace of MMT program has been slowed down and the focus of the National Working Group has been shifted to improve service quality to increase the retention and drug use.

32.6.3 MMT Programs Should Serve as a Comprehensive Service Platform

Drug dependence is a chronic disease with problems in many aspects, only provide methadone is not enough for client's rehabilitation. Psychosocial intervention and other medical interventions should be available to meet client's individual need. Due to shortage of professionals and other facilities, and not shortage of methadone, the MMT clinics cannot provide other services such as counseling, linkage to aftercare, and other treatments. This may be one of the important reasons for clients to drop out and use drugs during the treatment. Unlike MMT clinics in other Western countries, other pharmacotherapies such as buprenorphine, Suboxone, and naltrexone are also available as alternative choices. Methadone is the only choice for patients in China; no medications are available for patients who do not want to use methadone in China. Despite demonstrating the efficacy of buprenorphine and naltrexone, these trials have had a minimal influence on policy. A study of Suboxone has been conducted in Guangxi Zhuang Autonomous Region and Xinjiang Uygur Autonomous Region by the China CDC and local CDCs in collaboration with Johns Hopkins University. However, Suboxone produced by domestic or international company is still at clinical trial stage and is not available in Chinese market. It is predictable that Suboxone will serve as an alternative medication for opiate dependents within few years. Further research that examines the reasons for attrition and how the delivery of services can be improved is needed, and MMT program should serve as a platform of comprehensive intervention and offer more choices to meet individual needs of each patient.

32.6.4 Collaboration Among Multi-sectors

Drug addiction behavior is defined as illegal and can be sent to compulsory drug rehabilitation institution by public security system. The conflicting approach between "zero tolerance" policies toward drug use and harm reduction programs including MMT and a lack of cooperation among related departments may make it difficult for the effective implementation of MMT programs. Entry into the MMT program requires registration as a drug user with the public security system, and this may be a big barrier for patients since they do not want to be marked as "drug addicts" which is highly stigmatized in China. MMT clinics are required to report to the police patients who are drug positive for the third time. Clinics operated by law enforcement are likely to be stricter and less able to deviate from official guidelines than facilities that are operated by the public health system. Some patients who relapse in the MMT clinics were sent to compulsory drug rehabilitation center; therefore, many patients are scared to go to MMT clinics.

Significant progress has recently been made in this area and the public security system are being ever more supportive, especially of MMT, paving the way for faster scale-up of MMT programs. Health workers cannot expect law enforcers to ignore illegal behaviors, but they can work with them to find mutually agreeable strategies for achieving their respective goals. Synchronized drug use control approach, open communication, and strong cooperation among involved governmental departments are needed to ensure the effective implementation of MMT program in China. As a substantial number of drug users are incarcerated and a proportion of them are HIV positive, MMT program should be considered in incarceration centers to prevent further spread of HIV and drug use in the future.

32.6.5 Capacity Building for Staffs in MMT Clinics

Evidence-based treatment approaches for addiction are effective only when properly implemented and conducted. Compared with Western nations, MMT programs in China are still at an early stage of development. Staffs working in MMT have different backgrounds with different levels of professional capacity. The majority of MMT clinicians only received minimum professional trainings and lack sufficient expertise in managing pharmacotherapy treatment or in delivering psychosocial interventions. Drug addiction is a very complicated condition with multidrug use and complex comorbid physical or mental health problems, and well-trained treatment staffs are needed to deal with these problems. Studies have consistently indicated that methadone maintenance combined with psychosocial services is more effective in retaining patients, decreasing relapse rates, and reducing costs than maintenance treatment alone. But no standardized comprehensive psychosocial service or counseling is available for patients due to the shortage of professional capacity in China. Therefore, sustained and intensive professional trainings are needed to enhance the capacity of staffs in MMT programs. Institutional capacity building to deliver sustainable and standardized services will ultimately improve retention rates in China.

Despite the abovementioned challenges, the MMT programs in China have achieved tremendous progress. The evaluation of the ongoing MMT program has suggested reductions in heroin use, risky injection practices, and, importantly, criminal behaviors among clients and resulted in other positive outcomes. With the great determination and effort to control drug use and HIV transmission from the government, it is hoped that the coverage and quality of MMT program will be improved further and its treatment goal in the near future will be achieved.

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An Overview of Iran Drug Treatment and Harm Reduction Programs

33

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Contents

Abstract

The opioid addiction rate in Iran is among the highest in the world. One contributing factor is Iran's long border with the world's main opium producer, Afghanistan, with consequent extensive availability of opium and heroin. Following the 1979 Islamic revolution, drug policy employed in Iran was primarily based on a supply reduction rationale, with an aggressive criminal justice/

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incarceration response. This began to change as harm reduction programs in Iran were initiated in 2003. After an alarming increase in HIV infection among injection drug users and following a pilot study in 2002, methadone maintenance treatment became an accepted health policy and has been extensively implemented in Iran. Success of the Iranian harm reduction approach is based on attitudinal changes by policy makers, a rapid dissemination throughout the country, and implementation of programs by private sector people and NGOs. After successful implementation of methadone maintenance program in the country, buprenorphine maintenance was started since 2006. In 2011, opium tincture maintenance was initiated for those who are dependent to opium. Iran also has one of the most extensive methadone maintenance treatment programs within the prisons throughout the country. Currently, there are more than 2,500 agonist maintenance treatment units available in almost all large cities, providing treatment to more than 300,000 patients. In addition to the agonist maintenance centers and prisons, agonist therapy is available in drop-in centers and triangular clinics which are health centers run by public sector, where drug users have a free, voluntary HIV consulting and testing, free antiretroviral treatment, and needle syringe exchange program.

33.1 Introduction

Since centuries ago until the present time, psychoactive substances have influences on personal, sociocultural, religious, and even political aspects of Iranians' life. Wine, according to mythical stories and archeological excavations from 5400 BC, may have originated in Iran (McGovern 2003). It was a drink of choice for the upper class patricians in premodern times. Its use diminished temporarily after the introduction of Islam in the seventh century, but after a short period of time, people started drinking wine and its use continued to be popular but hidden until the present-day Islamic Republic (Matthee 2005). In ancient Iran (Persia), Mei (the Persian word wine) has been a central theme of poetry more than a thousand years, although alcohol is strictly forbidden in Islam. Shiraz, a very old city in Iran (1 h far from Persepolis), continued to be a center of wine production in Islamic era, and today, its name is on a very famous dry red table wine (Robinson 2006). Safavid dynasty permitted producing and exporting wine and also drinking it but not in public. It is interesting that Safavid kings were the most religious Iranian kings after Islam, but some of them died from alcoholism (Matthee 2005) (Fig. 33.1).

The eleventh century Persian poet Farrokhi has said: Although wine is forbidden, I believe that it becomes licit for lovers when spring arrives, God gives us his blessing as we drink. Come and don't regret it.

Opium was also a popular drug since Safavid dynasty (1502–1736) and became more popular during Qajar period (1785–1925).

Dr. Jacob Eduard Polak (1818–1891) – a Jewish Austrian physician who worked in Iran between 1851 and 1860 as a teacher of the first Iranian medical school – has

Fig. 33.1 Serving Wine in a Royal Ceremony in a Painting form Safavid Era

written in his book with the original title "Persien, das land und seine bewohner": "opium use is a very popular habit and it has no negative social stigma or shame for users. It is not forbidden and every Iranian who can afford its cost uses it daily... most people only took up the habit only in old age and stick to the same amount, so that effects tended to be minimal." Iranians began to develop a noticeable addiction to opium in the mid-ninetieth century. Although opium has existed in Iran in some form or another for centuries, widespread addiction was not known in the country until about 1860 (McLaughlin 1976).

33.2 Drug policy and Drug Treatment in Iran

33.2.1 From Over-Criminalization to Harm Reduction

The first treatment centers specialized for addiction and first outpatient methadone program in Iran initiated in the early 1970s. The first program was launched in 1974 in Shiraz city which used opioid agonist medication for assisted withdrawal of opioid-dependent clients. Before that there are reports of methadone use for

inpatient medically supervised assisted withdrawal for opioid treatment in Tehran. There was limited number of clients in this program which received methadone on maintenance basis.

All programs changed again to criminalization, moralization, and supply reduction after Islamic revolution in 1979. The situation continued in the same way until 1990s. By that time, the country political and health official realized that supply reduction and criminalization policy is not working. Drug offenders made up more than 50 % on the country prisoners, and drug flow from eastern borders was unchanged even with long border blockade. On the other hand, continuing conflicts in Afghanistan, the eastern neighbor of Iran, made it the main producer of opium which produces more than 90 % of global opium, and opium became cheaper and more easily accessible. At this time, Iranian Welfare Organization started first addiction treatment program after the revolution and launched outpatient addiction treatment centers in many cities across the country.

33.2.2 First National Epidemiological Studies

In order to have a real picture of substance abuse in the nation, the Iranian Welfare Organization in collaboration with the United Nation's International Drug Control Program (UNDCP) office performed a rapid situation assessment in a study from 1998 to 1999. According to the data of this study and other studies, authorities in Iran Drug Control Headquarters (DCHQ) and other officials believe that around 1,200,000–2,000,000 individuals living in Iran would have a diagnosis of drug abuse or drug dependence according to the DSM-IV criteria. The average Iranian addict is very likely male, married, and employed. Data from various provinces and within different groups show that more than 90 % of the drug-abusing population is male. In fact, the RSA study claimed that on average, 93 % of drug abusers in the nation are male, whether imprisoned, in treatment, or on the streets. The lowest preponderance of males belonged to Tehran, with 87 %. Around two-thirds of the addict population is married. This figure is lowest in Tehran, where only half seem to be married. Even in the incarcerated group, the majority (51 %) was married. In fact, less than 10 % of the addicts live alone; a spouse, parent, or sibling is usually present. Employment is also the rule in this group. Unemployed drug abusers comprise only a fifth of the population. According to study, a quarter of Iranian narcotic abusers have a history of intravenous (IV) injection of opioids, mainly heroin. Appearance of heroin injection dates back to 1960s. A study performed on 318 narcotic abusers with a lifetime history of IV drug abuse has shown that the average Iranian IV drug user (IDU) is 31.4 ($\pm$8.7) years of age, significantly 2 years younger than non-IDU; has started drug use around 3.5 years before non-IDUs (19.6 year vs 23.1 year); and has started injecting while 26.2 ($\pm$6.7) years old. Thus, injection of illicit drugs begins on average 7 years after its non-IV consumption. While the male-to-female ratio for non-IDU is 12:1, it is 31.3:1 for IDUs. More than half of the IDUs are single (Mokri 2002).

As opium production in neighboring Afghanistan has dramatically increased over the past decade, Iran has been impacted more than any other country (International Narcotics Control Board 2009; UNODC 2009a).

Although the vast majority of global opium seizures (83 %) take place in Iran, every year tons of opium flow from Afghanistan to the rest of the world, and the biggest share – 40 % – is through Iran. Iran faces many problems along its eastern border, and much of the country's supply reduction efforts are focused in this area. Global consumption of opium is estimated at 1,100 t per year, used by four million users; over 42 % is estimated to be used in Iran. It is estimated also that Iran consumes 17 t of heroin annually; this is 5 % of global consumption. Iran has the highest rate of abuse of opiates in the world (UNODC 2009b). Many adolescents in Iran, age of drug use onset, are under age 18 (Momtazi and Rawson 2010).

33.2.3 Methadone Maintenance Treatment (MMT) Programs

With the aim of adopting more effective strategies to address opioid use and HIV-related drug-using behavior among opioid-dependent population, the first methadone maintenance treatment (MMT) pilot project was conducted in Roozbeh psychiatric hospital, in August 2002 (UNODC 2005). It was a double-blind randomized, controlled trial comparing fixed doses of 40 and 70 mg daily oral methadone to treat opioid dependency. The result of the study indicated that MMT effectively reduced illicit opioid use and criminal and violent behavior and helps patient save a reasonable sum of money formerly spent on drug consumption. Three-month treatment retention among 40 mg, 70 mg, and total sample were 44, 74, and 54 %, respectively. Another multicenter, open-label study of individualized dose of methadone maintenance treatment showed dramatic improvement of illegal opioid use, injection, and mood and social and personal functioning indicators of opioid-dependent clients seeking help from Roozbeh hospital (Iranian National Center for Addiction Studies, since October 2003), West Triangular Clinic, and Persepolis drop-in center measuring by Opioid Treatment Index (Razzaghi et al. 2005).

The finding of abovementioned studies supporting feasibility, acceptability, and effectiveness of MMT led to adoption of MMT as a building block of drug treatment and HIV prevention programs for people who inject opioids by Ministry of Health (MoH) and DCHQ. By 2004, Substance Abuse Prevention and Treatment Office (SAPTO) of MoH developed the first protocol for MMT which included clinical guideline to provide the treatment, as well as regulations for establishment of opioid agonist treatment program referred as "agonist units" within substance abuse treatment centers. Certified drug treatment programs affiliated to public-owned, private, or nongovernmental organizations (NGOs) were allowed to establish MMT programs for 50 clients providing one multidisciplinary treatment team consisted of one trained general physician, one clinical psychologist, and two nurses. The opioid agonist treatment units could increase their MMT slots to 100 after 1 year of activity without any violation of regulations and providing

two multidisciplinary treatment teams. They also allowed increasing their MMT treatment slots to 200 after another year of activity and providing four multidisciplinary treatment teams and one social worker. For each 100,000 general population, one opioid agonist unit was allowed to establish, and they must have at least 1 km distance with each other.

Addiction treatment practitioners in Iran have had many decades of experiences with short-term assisted withdrawal of opioid dependents with clonidine or opioid medications before introduction of MMT at 2002. Initially some practitioner, clients, and their families preferred short-term withdrawal with methadone over long-term maintenance programs; however, gradually both practitioner and the clients realized that the methadone treatment should be long term to be successful. Newly established agonist units' slots were filled very soon, and waiting lists for entering to methadone maintenance programs were developed. At the end of 2004, 93 public-owned and 201 private agonist units were reported in 4,091 and 3,701 clients on MMT, respectively (Razzaghi et al. 2009).

To increase accessibility of methadone maintenance treatment, requirements for establishment of opioid agonist treatment were eased by second edition of the protocol which released in 2006 (SAPTO 2006) and other regulations issued by MoH in 2007. Currently certified outpatient drug treatment programs could establish an agonist unit for 100 MMT clients providing one multidisciplinary treatment team consisted of one trained general physician, one trained bachelor level psychologist or counselor, and one nurse as well as enough physical environments to deliver the program including one prescribing room, one counseling room, one distribution unit, and one waiting room. Agonist units could increase their MMT slots, if they provide enough staff and physical. The limitation of establishment of new agonist units in terms of the area population and distance from other agonist units has been removed for private sector.

The first methadone protocol devised the following inclusion criteria for MMT program: (1) diagnosis of opioid dependence according to DSM-IV-TR criteria, (2) using drugs through injection, (3) above 18 years old, and (4) written informed consent for treatment. Non-IV drug users were allowed to enter MMT only after psychiatrist visit verifying existence of at least one of following conditions: (1) chronic psychiatric comorbidity, (2) history of three documented failed treatment attempt in a client above 30 years old and at least 10 years of drug use history, (3) diagnosis of cluster B personality disorder, (4) female gender, or (5) history of imprisonment (SAPTO 2004). These criteria were aimed to increase availability of MMT for people who inject opioids who needed it more, but limited access to psychiatrist in some setting led to revision of them in the second methadone protocol (SAPTO 2006) as follows: (1) diagnosis of opioid dependence according to DSM-IV-TR criteria, (2) above 18 years old, (3) written informed consent for treatment, and (4) one of the conditions – (a) IV drug use, (b) heroin or crack heroin use, (c) opium users with history of three previous failed treatment attempt in a client with at least 10 years of drug use history, (d) HIV positive, (e) history of imprisonment, or (f) female gender.

Table 33.1 No. of MMT clients in community programs

Year	No. of clients on MMT in the community
2002	160
2003	1,133
2004	1,551
2005	7,792
2006	35,139
2007	66,126
2008	111,699
2009	158,975
2010	237,688
2011	283,019

The criteria for MMT programs aimed to increase treatment access for people who inject drugs or use heavier opioids such as heroin or crack heroin, but there has been a high demand for this program from people who use opium through swallowing or smoking. This shows that on one hand, MMT has been an acceptable intervention for Iranian opium users, but on the other hand, it has been a challenge for opioid treatment system in the country because opium users compete with heroin or injecting drug users to fill MMT slots which mainly provide by private sector without any insurance coverage (Mokri and Schottenfeld 2008). To address this issue, DCHQ supported MoH and Social Welfare Organization (SWO) to scale up public-funded, low-cost MMT programs provided for socially disadvantaged and homeless opioid users across the country in 2007. At the end of 2007, 173 public-owned and 587 private agonist units were reported in 15,983 and 50,191 clients on MMT, respectively (Noroozi et al. 2011). Table 33.1 presented number of MMT clients in community programs at the end of each year from 2002 to 2011.

There is no limitation on methadone dose or length of treatment in Iranian national protocol. MMT programs delivered through outpatient clinics must provide regular assessments and psychosocial interventions, although low-threshold MMT programs delivering through drop-in centers do not need to provide intensive psychosocial services and drug testing. Drop-in centers initially established to provide harm reduction services including needle, syringe programs (NSPs), wound care, HIV prevention, psycho-education, and support services including bath and warm meals for hard-to-reach homeless injecting drug users in suburb areas of Tehran and few large metropolitan areas in 2003. Treatment team in low-threshold MMT programs consisted of one trained general practitioner and one nurse which could provide services to 100 MMT clients. The low-threshold MMT clients do not benefit from privilege of take-home methadone doses. The number of MoH-funded drop-in centers and outreach teams established by NGOs increased from 12 and 12 in 2004 to 79 and 126 in 2007, respectively. The number of clients who received MMT in MoH-funded DICs during this time period increased from 886 to 4,114 (Razzaghi et al. 2009). Effectiveness of MMT provided

in DIC setting is documented in a multicenter open-label individualized dose of methadone among clients of one drop-in center in south of Tehran (Razzaghi et al. 2005). The total sum of drop-in centers funded by MoH and SWO reached to 150 in 2007 and has been stable since then.

An Iranian site – Iranian National Center for Addiction Studies (INCAS) – was among the study sites of World Health Organization (WHO) multi-country study which tested effectiveness of opioid substitution treatments (OSTs) in eight countries with very diverse availability of resources including China, Indonesia, Thailand, Lithuania, Poland, Ukraine, Australia, and Iran (Lawrinson et al. 2008). Two interesting findings of the study were as follows: (1) MMT can be effective consistently in a diverse range of settings in terms of cultural background and resources and (2) MMT not only can reduce illicit opioid use and HIV-related high-risk behavior associated with injection but also can significantly improve quality of life of the clients.

Data regarding the coverage of MMT program for people who inject drugs is not available. A cross-sectional study of 810 clients (95 % male; mean age, 40.5 year) on MMT in eight randomly selected private clinics in Tehran indicated that only 5 % of participants admitted injection drug use as their drug administration route (Shekarchizadeh et al. 2012). The first biobehavioral survey among people who inject drugs reported that 33 % of participants were on MMT (MoHME 2010). The second biobehavioral survey in people who inject drugs in 2010 indicated that 43 % of drug users with a history of drug injection during last 12 months were under MMT and had not injected during last month (Haghdoost et al. unpublished report; Ministry of Health and Medical Education 2012). A recent modeling study projected a shift in highest trend of HIV from people who inject drugs to female sex workers. It was estimated that new infected cases via unsafe sex will increase in the future, while over time, the trend with respect to transmission via unsafe injection will decrease, which could be attributed to implementation of evidence-based harm reduction programs particularly MMT among injecting drug users (Haghdoost et al. 2011).

A more recent study on injecting drug users recruited from referrals of seven drop-in centers in three provinces of Iran including Golestan, Alborz, and Isfahan showed that 63 % of participants "know somewhere to get low cost or free MMT," 42.2 % "received MMT in their lifetime," and 35.3 % "have been on MMT during last year" (Noroozi et al. 2012).

Despite these promising preliminary findings, there are limited data regarding the quality of MMT program at national level, and development of a monitoring and evaluation system to develop necessary data and provide timely feedback to the system is crucial for the future of the program.

33.2.4 Methadone Maintenance Treatment Program in Prisons

Although the frequency of drug use might decrease after imprisonment, the high-risk drug-using behavior including injecting drug use and shared injection will increase (Center for Education and Research of Prison Organization 2002). Methadone maintenance program has showed its efficacy in a randomized controlled

Table 33.2 No. of MMT clients in Prisons

Year	No. of clients on MMT in correctional settings
2002	100
2003	300
2004	1,423
2005	2,814
2006	8,048
2007	19,500
2008	25,400
2009	25,000
2010	28,826
2011	38,256

trial comparing individualized dose methadone plus counseling and psychiatric visits with counseling and psychiatric visits alone in an Iranian prison (Bayanzadeh et al. 2007). The study indicated that MMT significantly reduced drug use, injection, suicidal thoughts, and suicidal attempts as compared to baseline assessment, while no significant change in control group was detected. The methadone maintenance program was scaled up rapidly in the country, and currently, almost all medium- and large-size correctional setting in the country has methadone maintenance programs (Farnia et al. 2010). Table 33.2 presented number of MMT clients in correctional settings at the end of each year from 2002 to 2011.

Insufficient recourses to implement the program and limited access to continuation of MMT after release are among major problems of Iran MMT programs (Zamani et al. 2010). Discontinuation of treatment after release will negatively affect post-release treatment outcomes. The Prison Organization lunched some after care MMT program, but many prisoners might move to other cities after release and need continuation of the program in their place.

33.2.5 Buprenorphine

Ahmadi and his colleagues were the first who compared efficacy of different doses of sublingual buprenorphine for maintenance treatment of opioid dependence in Shiraz, Iran. They showed sublingual buprenorphine is safe and effective for maintenance treatment of opioid dependence in outpatient settings, and the treatment group which received higher daily buprenorphine dose (8 mg) had significantly higher retention rate as compared to lower doses groups (Ahmadi and Bahrami 2002; Ahmadi et al. 2004).

Buprenorphine has been approved to use for assisted withdrawal or maintenance treatment of opioid dependence since summer 2006. The previously certified "agonist units" were allowed to use buprenorphine without limitation for treatment slots. Although there is no insurance coverage or governmental support for buprenorphine program, there is a demand for it particularly from opioid users with less severe opioid dependence.

33.2.6 Tincture of Opium

To first pilot project of Tincture of Opium – an oral water/alcohol extract of opium containing 1 % morphine – for treatment of opium dependence was conducted in INCAS clinic in 2006 (Mokri et al. 2007). Twenty-two opium-using clients with history of an average daily opium use of 4.33 g stabilized on an average dose of 31.6 ml Tincture of Opium and followed for 6 months. Six-month retention rate was 71 % for all sample and 87 % excluding first-week dropouts. Improvement in familial and social scales but to a lesser extent was also noticed. Further studies showed safety and efficacy of Tincture of Opium as compared to methadone and effectiveness of it in two treatment models including maintenance treatment and gradual dose reduction combined with self-help programs including peer counseling and recreational activities initiated by Congress 60, an NGO for opium abusers. Since 2011, Tincture of Opium is also available for "agonist units" with at least 2 years of experiences with methadone and or buprenorphine and without history of violation of regulations. The half-life of the medication is about 8 h, and clients need to receive it in two divided dose, so agonist units were allowed to dispense afternoon take-home doses from the beginning of the treatment. The maintenance model of the program has not been accepted largely because there is no take-home dose for that and clients have to come to clinic for all of their morning doses. The program works best where the medication dispensed through clinic and peer counseling, and recreational activities developed by NGO for opium abuser, namely, Congress 60, are available.

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Opioid Agonist Diversion in Opioid-Dependence Treatment

34

Hannu Alho

Contents

Abstract

Diversion is defined in this publication as unauthorized rerouting or use of a substance, and abuse is defined as any use of a prescription drug that deviates from medical practice. This refers to the manner in which medication is used such as snorting, injecting, taking excessive quantities, or combining it with other substances for intoxicative purposes.

Diversion and abuse of pharmacotherapy used in opioid-dependence treatment can have a serious negative impact on public health at the individual and societal level. Diversion can lower the credits of treatment services through increased morbidity and mortality and economic burden through lost productivity and unemployment. Diversion is a global problem, but most studies and concerns arise from the USA, Australia, and Northern Europe. While existing

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evidence confirms the occurrence of this issue, standardized indicators are missing and the phenomenon is not uniformly appreciated by prescribers and policy makers.

Most publications of diversion and abuse report the mortality rates associated with the diversion and abuse of methadone and prescription opioid analgesics. The reports of fewer buprenorphine-related deaths compared with deaths associated with methadone can be attributed to buprenorphine's pharmacology and ceiling effect on respiratory depression. However, deaths due to asphyxia as well as following acute poisoning with severe respiratory depression have recently been attributed to buprenorphine in opioid abusers. The abuse prevalence and injection of buprenorphine tablets are reported in worldwide publications addressing the harms associated with it. Several studies indicate that inability to enter opioid maintenance or substitution treatment could be a significant contributor to diversion. In addition, studies are challenging the often-held view that regulation and restricted access are necessary to ensure the safety of individuals using opioid agonists' medications.

To lower the diversion and develop strategies to avoid abuse, it is important therefore to examine and understand the reasons of it. One of the most important strategies to avoid diversion is good quality of the treatment and treatment outcomes. Some pharmacotherapies may have lover diversion potentiality, but the key factor is patient confidentiality and good quality of treatment.

34.1 Introduction

Opioid dependence is widely recognized to be a chronic relapsing condition (Goldstein and Herrera 1995; Fiellin and O'Connor 2002; O'Brien 1996; Cami and Farre 2003) that requires long-term treatment to achieve positive clinical outcomes. Untreated opioid dependence harms the individual and society through increased mortality (Kimber et al. 2010; World Drug Report 2012), increased risk of blood-borne virus (BBV) transmission associated with injection drug use (Kimber et al. 2010; Altice et al. 2011), poor social functioning (De Maeyer et al. 2010), loss of economic productivity (Hansen et al. 2011), and criminal justice expenditure (Hansen et al. 2011).

Most common substances (though not exclusively) related to diversion and abuse of opioid pharmacotherapies and opioid-based formulations in the treatment of opioid dependence are methadone, Polamidone (trade name of R-methadone), buprenorphine, buprenorphine/naloxone, codeine, slow-release oral methadone, and slow-release oral morphine. However, significant diversion/abuse related to other divertible prescription medications including benzodiazepines and opioid-based painkillers is not included in this paper.

Definition for diversion can be defined as the unauthorized rerouting or appropriation of a substance (Merriam–Webster's Dictionary of Law 1996). Abuse is defined as any use of a prescription drug that deviates from medical practice. This refers to the manner in which medication is ingested such as snorting,

injecting, taking excessive quantities, or combining it with other substances for intoxicative purposes (American Psychiatric Association 2004).

34.2 Features of Diversion

34.2.1 Consequences of Diversion

Though strong evidence indicates that diversion and abuse is occurring, a global understanding of the consequences is missing or the issue is varied. The impact of consequences on public health can be used to raise awareness of this issue, identify regional epidemiological trends across globe, and drive management strategies in opiate maintenance area. The most well-known consequences include:

- Increased patient morbidity and mortality (Centers for Disease Control and Prevention 2010) through an increased risk of:
  - Overdose/fatal respiratory depression (Laberke and Bartsch 2010; Perret et al. 2000)
  - Nonfatal overdose and related emergency admissions (Centers for Disease Control and Prevention 2010)
  - Contracting blood-borne viruses such as HIV and hepatitis C (HCV) (Center for Disease Control and Prevention 2011; Berson et al. 2001)
  - Complications associated with injection drug use including limb ischemia, tissue necrosis, and endocarditis (Ho et al. 2009a)
- A negative impact on prescribers' practice (Noroozi and Mianji 2008)
- Threatened reputation of treatment services and compromised public acceptance of long-term treatment of opioid-dependent individuals (Noroozi and Mianji 2008).

34.2.2 Indicators of Diversion

In the absence of standardized indicators of diversion and abuse of opioid pharmacotherapy, the following impact measures should be considered:

- Mortality associated with abuse and diversion
- Incidence of injection complications (site reactions, amputations)
- Contribution of injecting drug use to HIV transmission
- Contribution of injecting drug use to HCV transmission
- Role of methadone and buprenorphine injection in hepatic complications
- Patterns of abuse (including injection drug use) in relation to drug availability

34.2.3 Strategies to Limit Diversion

A 2010 survey of European physicians found that despite acknowledging that diversion and abuse was their responsibility, it was the most difficult area of

opioid-dependence treatment to manage (Bacha et al. 2010). To limit the diversion of pharmacotherapy used in opioid-dependence treatment, several countries have implemented regulations stipulating administration of doses under direct supervision in specialized clinics or pharmacies. However, such policies may restrict access to treatment, which in turn may fuel the demand for diverted opioid pharmacotherapy and increase the harms and financial burden of untreated opioid dependence (Bell 2010). While the use of abuse-deterrent formulations including volume-expanded methadone and buprenorphine-naloxone has been introduced to reduce diversion and abuse while maintaining treatment access, large-scale studies are needed to confirm its efficacy for this purpose.

34.2.4 "A Better Approach", Defining Treatment Outcomes in Opioid Dependence (OD)

Mitigation of diversion and abuse of opioid pharmacotherapy by the treatment community is of key importance, as it can pose significant risks to patients, physicians, and the availability of treatment in the future. However, treatment outcomes may play a key factor in management of diversion (Subata et al. 2013). There are currently two major limitations in the way outcomes data for opioid-dependence treatments are collected. Firstly, there is no standardized set of outcomes measures, so the quality of outcomes measurement will vary by country, region, and on an individual center basis. Secondly, this lack of outcomes standards means that collecting comparative information to compare outcomes between countries is difficult. These difficulties are highlighted by the situation in Europe. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) currently collates and reports data collected by individual countries; however, the variability in the outcomes measured and irregularity in country reporting can create issues.

In order to identify appropriate outcomes measure, it is important to look at various aspects of the treatment including the patient population, treatment goals, and setting. One single metric cannot quantify the range of outcomes of opioid-dependence treatment. Instead, a set of metrics are needed to capture mortality in treatment, individual and societal benefits, as well as harm-related outcomes. In addition, because opioid-dependent populations are highly variable in terms of their clinical presentation and their personal goals for therapy, there needs to be some flexibility in scoring success. Therefore, population or system-wide outcomes measurement in OD management should be based on a scorecard of a number of metrics.

Increasing access to OD treatments calls for better understanding of the impact of treatment outcomes to diversion. A range of measures describe effectiveness and long-term safety of buprenorphine and methadone in opioid-dependence management; however, there is a need for a universal or at least European system, to allow comparison at the "above-individual-patient" level.

34.2.5 Patterns and Prevalence of Diversion

Despite evidence demonstrating that abuse and diversion does happen, there is increasing consensus that considers diversion to be noncompliance and a sign of suboptimal treatment. The majority of studies related to diversion relate to patterns and rates of injection drug use and injection drug use-associated mortality. Methadone has been the most researched opioid pharmacotherapy for both lead impact measures, followed by buprenorphine, hydrocodone, and oxycodone. However, despite association with potential hepatic complications in clinical studies, few studies can be identified suggesting a role for methadone or buprenorphine in hepatic complications. The majority of diversion studies per product derived from the USA, followed by Australia. Data from the USA largely focused on the diversion and abuse of prescription opioid analgesics, in addition to opioid-dependence pharmacotherapy. In regions demonstrating a paucity of research/publications such as southern Europe, Asia (excluding Singapore), and Pacific countries, those identified focused on the diversion and abuse of methadone and buprenorphine. Reports from South Asia indicate that prescribing for pain is inadequate. There is a paucity of data across South Asia regarding the extent of diversion and abuse, although the problem is widely acknowledged. There is also a significant lack of treatment facilities across the region, as well as HIV awareness and needle-syringe programs (Larance et al. 2011).

In general, studies have shown that around 70 % of those injecting medication are self-treating, either due to inability to access treatment or suboptimal therapeutic dosing (Alho et al. 2007; Courty 2009). A post marketing surveillance study (2003–2007) from the USA indicated that there were steady increases in the rates of abuse, misuse, and diversion of both methadone and buprenorphine. Rate ratios (per 100,000 population quarter) of abuse, misuse, and diversion were consistently higher for methadone than buprenorphine (Dasgupta et al. 2010). A global literature review (Degenhardt et al. 2011) on mortality among dependent or regular opioid users across regions, according to specific causes, and related to a number of demographic and clinical variables demonstrated that overdose was the most common cause of death, with a crude overdose mortality rate 1.71 times higher in men than women. Out-of-treatment periods had 2.38 times higher mortality risk than in-treatment periods ($p < 0.0005$). Higher prevalence of opioid injection was associated with higher mortality rates. Retrospective data analysis (Laberke and Bartsch 2010) of methadone-associated deaths in Zurich, Switzerland, showed that most of the detected deaths occurred during illicit intake of methadone and high percentage of cases involved polydrug intoxication (76 %). An epidemiological review from the USA indicates that deaths from unintentional drug overdoses in the USA have risen steeply since the early 1990s and are the second leading cause of accidental death, with 27,658 such deaths recorded in 2007. The increase has been propelled by a rising number of overdoses of opioids, which caused more deaths than heroin and cocaine combined in 2007 alone (Okie 2010).

In Europe, diversion is a common problem, and a 2010 European survey of 300 physicians who treat opioid dependence found that diversion was a significant problem for 72 % of respondents (Bacha et al. 2010). Indeed, a wealth of data demonstrates that many opioid pharmacotherapies, particularly those used in the treatment of opioid dependence, are diverted and abused. For instance, in 2006, up to 25 % of French buprenorphine doses were diverted onto the black market (International Narcotics Control Board 2011); in Finland, over 70 % of the street drug users (IDUs), the primary drug was buprenorphine (Simojoki and Alho 2008); in Germany, 80–85 % of injecting drug users reported finding it easy to access methadone and buprenorphine on the black market (Simojoki and Alho 2008); and in Austria, according to a 2010 publication, diverted slow-release oral morphine was dominating the Austrian black market (Wickert et al. 2009).

A prospective cross-sectional study (Beer et al. 2010) from Australia demonstrates that on currently injecting drug users (IDUs), more than 10 % of participants reported buprenorphine as the drug they had most often injected, and 32 % had injected buprenorphine at least once in the 3 months before the interview. Frequency of sharing a used needle was also associated with buprenorphine injection, but HCV exposure was not (Beer et al. 2010; Aitken et al. 2008). In Australia, opioid diversion to the black market occurs in proportion to the amount of nonsupervised consumption, and inversely to heroin availability. Adverse consequences of diversion include opioid overdose fatalities, increased incidence of addiction (particularly in jurisdictions where heroin is scarce), and compromised public acceptance of long-term opioid prescribing (Bell 2010). Retrospective data analysis from Singapore with patients presenting with medical complications of buprenorphine abuse showed that since the introduction of buprenorphine for opioid-dependence treatment in 2002, there was a significant increase in IV abuse that led to life-threatening medical complications including infective endocarditis and cardiac failure. This study identified pulmonary hypertension as a potential comorbidity among IV buprenorphine users (Jenkinson et al. 2005; Chong et al. 2009). Nearly half of patients died as a result of their complications (Jenkinson et al. 2005).

To address the increased incidence of buprenorphine diversion and abuse, buprenorphine was combined with naloxone in sublingual tablet formulation (buprenorphine-naloxone combination). Injection of the combined product was planned to cause withdrawal symptoms and thus acting as a deterrent to abuse. Data is controversial, research from Australia indicates that patients receiving medication-assisted therapy (MAT) buprenorphine-naloxone combination product were injected less frequently than buprenorphine, especially when corrected for medication availability; injection of buprenorphine was more likely in those injecting other prescription opioids (Ho et al. 2009b). Data from Canada shows that among treatment-seeking opioid-dependent individuals characterized with buprenorphine-naloxone diversion practices, 100 % had diverted buprenorphine-naloxone to modulate opiate withdrawal symptoms arising from attempted "self-detoxification," with insufficient funds to purchase preferred illicit opioids, or inability to find a preferred source of drugs. A small study in Italy (Degenhardt et al. 2009)

evaluating the use of buprenorphine-naloxone for treatment of opioid-dependent patients after therapeutic switch from buprenorphine alone showed that only 2 % of patients attempted the intravenous abuse of the combined product, none of whom experienced any gratifying effects. A recent long-term follow-up study from Finland indicates that the street value of buprenorphine-naloxone product is 30–40 % less than the corresponding amount of mono-buprenorphine (Montesano et al. 2010).

34.2.6 Discussion

Diversion and abuse poses a significant risk to opioid-dependent individuals including increased overdose mortality, risk of blood-borne viral transmission, and medical complications associated with intravenous drug use. Diversion has very likely a negative impact on society through influence on prescribers, compromised integrity of treatment services, and a potential increase in societal aversion to the treatment of opioid dependence. While these well-known consequences often describe diversion and abuse, there is increasing consensus that diversion can be a sign of noncompliance and a sign of suboptimal treatment. A paucity of qualitative information and assessment of standardized indicators of diversion and abuse was noted. This may be due to the illicit nature of practices associated with this issue, making quantitative or qualitative data gathering difficult. In addition, geographical distribution of the publications per impact area and per product was uneven, with the majority originating from the USA and Australia. Research into diversion and abuse of prescription opioids has been based mainly in Central and Northern Europe, although an uneven geographical distribution within these regions was also identified.

Legal and regulatory measures to counter diversion and abuse by restricting availability of opioid pharmacotherapy can often serve to decrease treatment access. This can put opioid-dependent individuals at risk of further harm because drug users often buy diverted pharmacotherapies in an effort to self-treat their condition. However, treatment outcomes may play a key factor in management of diversion.

An alternative strategy is the use of opioid pharmacotherapy formulated to deter abuse. However, the impact of abuse-deterrent formulations on the extent of diversion and abuse is not fully clear. The overall number of prevalence of diversion and abuse of buprenorphine was greater than those relating to methadone diversion. Reported prevalence of buprenorphine diversion was higher (15.3–73 %) compared with methadone diversion (4.3–55 %). In addition, the lifetime prevalence of buprenorphine diversion and abuse was higher than that for methadone. This supports previous observations that buprenorphine is abused in many countries and may be more widely diverted than methadone.

Comparison of the numbers of publications relating to this issue in the USA, Australia, and all European regions suggests buprenorphine is more significant issue in European markets. The majority of publications identified are based on

studies which were conducted in the USA and Australia. This could be due to that in the USA, the Drug Abuse Warning Network (DAWN) (Drug Abuse Warning Network 2011) monitors drug-related visits to hospital emergency departments and drug-related deaths investigated by medical examiners and coroners. Emergency department data is published biannually. Mortality data is published annually, and additional analyses are available during the year. DAWN collects detailed drug data including that for illicit substances, prescription medication, and over-the-counter remedies. The Australian Illicit Drug Reporting System (2009) and the Ecstasy and Related Drugs Reporting System have operated in all jurisdictions since 2000 and publish annual reports of trends associated with illicit drug use (including heroin, amphetamines, cocaine, and cannabis). Trends are extrapolated from three data sources: interviews with injecting drug users, interviews with key experts who regularly encounter illicit drug users, and existing indicator data sources relating to illicit drug use.

Large proportion of publications per impact area is related to methadone-associated mortality (Perret et al. 2000). Evidence shows that methadone diversion is associated with a high risk of mortality due (Reynaud et al. 1998) to its full opioid agonist profile, effect on respiratory depression, and multiple drug interactions leading to increased plasma levels of methadone and toxicity. In addition, a long elimination half-life (24–36 h) may increase the risk of fatal overdose due to excessive intake and dose accumulation in the body. The high mortality risk attributed to methadone is supported by the high numbers of emergency calls for overdose or accidental exposure of children to methadone and the numbers of deaths in which methadone has been implicated, either alone or in combination with other substances (Rainey 1986; Gibson and Degenhardt 2007). It has been thought that the increase in methadone mortality may result from inappropriate prescribing to patients who have risk factors or indicators for abuse and increasing use of methadone as a low-cost analgesic by inexperienced prescribers. Even when buprenorphine may be more widely diverted than methadone (Ho et al. 2009b; Reynaud et al. 1998), buprenorphine-based treatment seems to be associated with fewer fatalities than methadone (Rainey 1986; Kim et al. 2012; Winstock et al. 2008).

However, there is clear and increasing evidence of harm associated with the diversion of prescription opioid analgesia. This phenomenon appears to be somewhat specific to the USA as the greatest number of publications relating to oxycodone, and hydrocodone in particular, originate from this region and are second only to methadone. In addition, the prevalence of prescription opioid analgesic abuse reported by publications from this region ranged from 72 % to 75 % (Gibson and Degenhardt 2007). In accordance with the trends in prescription opioid mortality, data shows an increasing prevalence of opioid analgesic abuse in rural and urbanized regions in the USA (Gibson and Degenhardt 2007).

Although buprenorphine maintenance therapy is associated with significant benefits including decreased HIV risk behavior and lower risk of fatal overdose (Rainey 1986) compared with methadone (Kim et al. 2012), injection of buprenorphine is associated with potentially fatal harms, as cutaneous

complications (Ho et al. 2009a), infective endocarditis (Jenkinson et al. 2005), and by mixing buprenorphine with other drugs including alcohol and benzodiazepines can be dangerous and may lead to fatal overdose (Bell et al. 2009). The injection of the combined buprenorphine-naloxone product was designed to cause precipitated withdrawal in opioid-dependent individuals, thereby acting as a deterrent to abuse. Although data suggest that injection rates of buprenorphine-naloxone are significantly lower than rates of mono-buprenorphine injection (Ho et al. 2009b), and the street value of the combination product is significantly less than corresponding mono-product (Montesano et al. 2010), further epidemiological studies are needed to determine whether the combination product is effective in deterring diversion and abuse. Buprenorphine has been considered being less fatal in overdosing because of its ceiling effect; however, recent studies show that buprenorphine's metabolite, norbuprenorphine, is assessed as being a potent respiratory depressor in rodents. Recently, norbuprenorphine, in contrast to buprenorphine, was shown in mice and in vitro to be a substrate of human P-glycoprotein, a drug-transporter involved in all steps of pharmacokinetics including transport at the blood-brain barrier (Havens et al. 2007). Even a major role for drug-drug interactions that can lead to P-glycoprotein inhibition in buprenorphine-associated fatalities and respiratory depression, there is no proof that buprenorphine can cause fatal poisoning except on children (Alhaddad and Cisternino 2013).

34.2.7 Key Messages

- Diversion and abuse of opioid-dependence pharmacotherapy is a significant worldwide public health issue.
- Adverse consequences include overdose fatalities, increased incidence of dependence, and compromised public acceptance of long-term opioid prescribing.
- Monitoring is essential to assessing prevalence and practices associated with diversion and abuse in order to direct national strategies aimed at neutralizing the problem.
- Treatment outcomes and good quality of treatment are key factors preventing diversion.
- Treatment restrictions policies may restrict access to treatment, which in turn may fuel the demand for diverted opioid.
- While additional large-scale epidemiological studies are required to confirm efficacy in reducing diversion and abuse, existing data is promising.
- The main observations on diversion of pharmacotherapies used for treatment of opiate dependence include:
  - Methadone abuse is widespread and is injected and diverted for recreational use.
  - Diverted methadone contributes significantly to the methadone-related death toll.
  - Diversion of slow-release oral morphine has begun dominating the Austrian black market.

- Buprenorphine alone is widely abused in many countries.
- Buprenorphine may be more widely diverted than methadone.
- Buprenorphine-based treatment is associated with fewer fatalities than methadone.
- Buprenorphine is associated with a lower risk of mortality compared with full agonist opioid treatments like methadone and morphine and may less unlikely to cause fatal overdose when ingested by opioid-naive individuals.
- Mixing buprenorphine with other drugs including alcohol and benzodiazepines can be dangerous and may lead to fatal overdose.
- Combination buprenorphine/naloxone product may have a lower abuse potential than other opioid pharmacotherapies.
- There is no research yet on the diversion of film or long release formula of buprenorphine.

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Addiction to Hallucinogens, Dissociatives, Designer Drugs and "Legal Highs" 35

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Contents

Abstract

Hallucinogenic drugs have as their primary effect the production of disturbances of perception. Hallucinogens can be classified according their chemical structure as: indoleamines (similar to serotonin), phenethylamines (similar to catecholamines), dissociatives (phencyclidines) and others (including salvinorin, dextromethorphan, muscarinic antagonists and cannabinoids). The hallucinogenic effects appear to be related to the agonistic action on 5-HT2A receptors in the cortex. Ketanserin, a 5-HT2 antagonist, blocks some of the specific effects of LSD and other hallucinogens. It also activates the dopaminergic receptors and

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causes a glutamatergic activation. All these actions seem to cause a functional imbalance at various levels (cortical areas, the limbic system, which is a group of brain structures involved in emotional regulation), contributing to distortion of the integrative action. The novel psychoactive substances (NPS) can induce substance use disorder, intoxication and in some cases withdrawal syndrome (for those with psychostimulant properties). Depending on the substance and pharmacological effects, the DSM-V diagnostic criteria for hallucinogens or stimulants can be applied (American Psychiatric Association 2013).

The therapeutic aim in these cases is to reduce consumption and achieve abstinence. In some cases of NPS cessation can be easy because there is no physical dependence; in other cases (with more of a psychostimulant profile) some symptoms of withdrawal syndrome can be observed. There are no specific drugs for treating the disorders caused by these substances.

35.1 Introduction

This chapter is a review of the different families of hallucinogenic, dissociative and novel psychoactive substances. It provides a brief historical introduction, the origins, chemistry and mechanism of action, the pharmacological and adverse effects, and the relevant psychiatric clinical aspects.

35.2 Hallucinogens, Dissociatives and New Psychoactive Substances

35.2.1 Classical Hallucinogens

Hallucinogenic drugs have as their primary effect the production of disturbances of perception, thought, or mood at low doses, with minimal effects on memory and orientation. A hallucination is defined as a sensory perception without objective reality. An illusion is a perceptual distortion of an actual stimulus in the environment; it is a distortion of what is perceived. Hallucinations can develop in any sensory modality, but are most commonly visual or auditory in nature.

Subjects with hallucinations induced by acute consumption of a hallucinogenic are aware that the experience is caused by the substance, and are able to maintain a sense of reality. There are a variety of widely accepted synonyms for the hallucinogens, including the term psychedelic, and psychotomimetic.

Hallucinogens include a diverse group of substances with different chemical structures. Hallucinogens can be classified (Table 35.1) according their chemical structure as: indoleamines (similar to serotonin), phenethylamines (similar to catecholamines), dissociatives (phencyclidines) and others (including salvinorin, dextromethorphan, muscarinic antagonists and cannabinoids). Hallucinogens can be found naturally in some plants, animals, and can be synthesised in the laboratory. Some hallucinogenic drugs are included in the category of designer drugs, legal highs and new psychoactive substances (Camí and Farré 2003).

Table 35.1 Classification of hallucinogens

Indole amides	**LSD derivatives**	Lysergic acid amides: ergine, isoergine
		Lysergic acid diethylamide (LSD-25 or lysergide)
	Substituted tryptamines	Psilocybin
		Psilocin
		O-Acetylpsilocin (4-acetoxy-DMT)
		Diethyltryptamine (DET)
		Bufotenine (cebilcin, 5-OH-DMT) Dimethyltryptamine (DMT)
		5-bromo-*N*,*N*-dimethyltryptamine (5-Bromo-DMT)
		5-methoxy-*N*,*N*-dimethyltryptamine (5-methoxy-DMT)
		5-methoxy-dimethyltryptamine (5-MeO-DMT)
		Ibogaine
		Ayahuasca (contain DMT)
Phenethylamines	**Methoxyamphetamines "hallucinogenic amphetamines"**	Mescaline (3,4,5-trimethoxyphenethylamine)
		4-bromo-2,5-dimethoxyamphetamine (DOB)
		4-methyl-2,5-dimethoxyamphetamine (DOM, serenity-tranquillity-peace or STP)
		2,4,5-trimethoxyamphetamine (TMA-2)
		Paramethoxyamphetamine (PMA)
		4-bromo-2,5-dimethoxyphenylamphetamine (2CB-MFT)
		2,5-dimethoxy-4-bromo-phenethylamine (2-CB, nexus)
		2,5-dimethoxy-4-iodophenethylamine (2-C-I)
		2,5-dimethoxy-4-ethylthiophenethylamine (2C-T-2)
		2,5-dimethoxy-4-(n)-propylthiophenethylamine (2C-T-7)
		8-bromo-2,3,6,7-benzo-dihydrodifuran-ethylamine (2-CB-Fly)
		Bromo-benzodifuranyl-isopropylamine (bromo-dragonfly)

(*continued*)

Table 35.1 (continued)

	Methylenedioxyamphetamines "entactogen amphetamines"	3,4-methylenedioxymethamphetamine (MDMA, "ecstasy", "Adam")
		3,4-methylenedioxyamphetamine (MDA, "love pill"),
		3,4-methylenedioxyethylamphetamine (MDEA or MDE, "Eve")
		N-methyl-1-(3,4-methylenedioxyphenyl)-2 butamine (MBDB)
		3,4-methylenedioxymethcathinone (methylone, "explosion")
		3,4-methylenedioxyethylcathinone (ethylone)
		β-keto-*N*-methylbenzodioxolylpropylamine (bk-MBDB, butylone)
Dissociatives (Phencyclidines)	Phencyclidine (PCP)	
	Ketamine	
	Methoxetamine	
	3-methoxy-phencyclidine (3-MeO-PCP)	
Others	Opioid derivatives	Dextromethorphan
	Anticholinergics	Atropine, scopolamine, trihexyphenidyl
	Salvinorin A	
	Thujone	
	Muscimol and ibotenic acid	
	Cannabinoids (natural and synthetics)	

35.2.1.1 Origin and Synthesis

Hallucinogens are as old as civilisation. Many cultures recorded eating certain plants specifically to induce visions or to alter the perception of reality. Often these hallucinations were part of a religious or initiation experience. In this context they are referred to as entheogens. Shamans in Siberia were known to eat the hallucinogenic mushroom *Amanita muscaria*. The ancient Greeks also used naturally occurring plant hallucinogens. Peyote, a cactus found in the southwestern United States and Mexico was used by native peoples, including the Aztecs, to produce visions.

The modern synthetic drug era began in the late 1930s with the synthesis of lysergic acid diethylamide (LSD) by the Swiss chemist, Albert Hoffman. While working at Sandoz Laboratories, Hoffman synthesised LSD as part of an effort to develop ergot derivatives capable of reducing post-partum bleeding. Some years later, after accidentally absorbing a small amount, he experienced its psychoactive effects while bicycling home. After World War II there was an explosion of interest in hallucinogenic drugs in psychiatry, either in their potential for psychotherapeutic applications or in their use in producing a "controlled psychosis", in order to understand psychotic disorders. It was marketed by Sandoz laboratories under the trade name Delysid® as a potential tool for psychotherapy in the 1950s. The growing

popularity of LSD in the 1960s associated with the hippie movement resulted in its ban in the United States in 1967. In recent years, there has been new interest in the investigation of the therapeutic use of hallucinogens (Hill and Thomas 2011).

35.2.1.2 Epidemiology and Pattern of Consumption

Hallucinogen use has declined since the 1970s, with the annual prevalence remaining below 10 % (Johnston et al. 2008). The types of hallucinogens used have also changed. LSD, which was the most widely used hallucinogen, has been surpassed by psilocybin and newer synthetic drugs. Today, the majority of LSD is synthetic. However, it can be derived from two naturally occurring substances, morning glory seeds (*Rivea corymbosa*) and *Claviceps purpurea* (a parasitic fungus), which contains some alkaloids, called ergot, as ergine and ergonovine. Synthetic LSD is crystalline. It is a white, odourless, tasteless powder that is dissolved and administered orally, sublingually, intramuscularly or intravenously. Sublingual formulations include postage stamps, chewing gum or sugar cubes, often decorated with new age symbols. Other hallucinogens are usually taken orally (mescaline, psilocybin, ayahuasca), smoked (DMT, salvia) or snorted (DMT).

European data show that among young adults (aged 15–24 years), the prevalence of LSD use at some point of life in Europe ranges from 0 % to 5.2 %, and is more common in the Czech Republic and Scotland, with prevalence of use in the past 12 months of 2.2 %. The prevalence of drug use in the past month was 1.2 %. The overall prevalence levels of hallucinogenic mushroom use in Europe have been generally low and stable for a number of years. Among young adults (aged 15–34), national surveys report last-year prevalence estimates for the use of hallucinogenic mushrooms to range from 0 % to 2.2 % (European Monitoring Centre for Drugs and Drug Addiction 2013b).

The lifetime prevalence of LSD use in the United States in students in the 12th grade is between 3.8 % and 4 % in the past 3 years (Johnston et al. 2013a). The trend in annual prevalence in young adults (30 years) is lower, between 0.2 % and 0.9 % in the last 3 years (Johnston et al. 2013b).

In the United States, of all substance use disorders, other hallucinogen use disorder (excluding dissociatives) is one of the rarest. The 12-month prevalence is estimated to be 0.5 % among 12- to 17-year-olds and 0.1 % among adults aged 18 and older in the United States. Rates are higher in individuals younger than 30 years, with the peak occurring in individuals aged 18–29 years (0.6 %) and decreasing to virtually 0.0 % among individuals aged 45 and older (Johnston et al. 2013a). A higher trend in lifetime prevalence of other hallucinogens in young adults (12.6–11.1 % over the past 3 years) (Johnston et al. 2013b).

Past-year prevalence is higher in clinical samples (19 % in adolescents in treatment). Among individuals currently using hallucinogens in the general population, 7.8 % (adult) to 17 % (adolescent) had a problematic pattern of use that met criteria for past-year other hallucinogen use disorder.

Among select groups of individuals who use hallucinogens (e.g. recent heavy ecstasy use), 73.5 % of adults and 77 % of adolescents have a problematic pattern of use that may meet other hallucinogen use disorder criteria. There are no prevalence

estimates of hallucinogen persisting perception disorder. Initial prevalence estimates of the disorder among individuals who use hallucinogens are approximately 4.2 % (American Psychiatric Association 2013).

35.2.1.3 Mechanism of Action

The reported similarity of psychic experiences elicited by the phenethylamines and the indolealkylamines, as well as cross-tolerance between the two classes (Winter 1971), suggested a shared mechanism of action. With advances in molecular biology, 14 distinct serotonergic receptors comprising seven families (serotonin-1–7) were discovered. Determining which receptors mediate the psychoactive effects, however, presented a challenge (Barnes and Sharp 1999). LSD is an extremely potent substance; active doses are between 0.5 and 2 μg/kg (100–150 μg per dose). Its activity is predominantly on serotonin (5-HT), but also on dopamine receptors. LSD, like other classical hallucinogens, is a partial agonist at serotonin 5-HT2 receptors, and also at the 5-HT1A/1C receptors, both presynaptic and postsynaptic. There is a good correlation between the relative affinity of these compounds for 5-HT2 receptors and their potency as hallucinogens in humans (Abanades et al. 2004; Sharp et al. 2007).

The hallucinogenic effects appear to be related to the agonistic action on 5-HT2A receptors in the cortex. Ketanserin, a 5-HT2 antagonist, blocks some of the specific effects of LSD and other hallucinogens. It also activates the dopaminergic receptors and causes a glutamatergic activation. All these actions seem to cause a functional imbalance at various levels (cortical areas, limbic system, which is a group of brain structures involved in emotional regulation); contributing to distortion of the integrative action. At a peripheral level ketanserin acts as a serotonergic antagonist and also in the dopaminergic system (D1 and D2 at least), and in the alpha adrenergic system. Most classical hallucinogens share the actions of LSD, but dissociative anaesthetics and dextromethorphan are NMDA receptor antagonists (*N*-methyl-D-aspartate or NMDA) (Vollenweider and Kometer 2010; O'Brian 2011; Sanders-Bush and Hazelwood 2011) and salvinorin A is a potent kappa-opioid receptor agonist. Some anticholinergic derivatives (*Amanita muscaria* mushroom, plants containing atropine derivatives) at high doses can induce intoxication with hallucinations owing to their action as antagonists of the muscarinic receptor in the CNS.

35.2.1.4 Acute Effects

Lysergic acid diethylamide(LSD) is well absorbed by the gastrointestinal tract. It is rapidly metabolised and only 1 % of the dose is excreted in urine without being biotransformed. It undergoes hydroxylation (with the addition of a group OH) and conjugation with glucuronic acid in the liver. Its half-life is about 3 h (range 2–5 h), but its effects last longer. The most sensitive analytical methods for detecting the use of LSD through the urine can be used up to 24 h after its consumption (Passie et al. 2008; Jones 2009).

Psychoactive effects peak at 2–4 h and can last for up to 12 h depending on the dose, tolerance, body weight and age. Users of LSD typically experience autonomic symptoms within a few minutes and psychoactive effects approximately 10 min later. The autonomic symptoms are mainly sympathomimetic, such as elevated

blood pressure and pulse, diaphoresis, piloerection, nausea, hyperreflexia and tremor. Anisocoria (unequal pupils) and hippus (rhythmically dilating pupils) are not uncommon (Schiff 2006).

Sensory effects generally appear 1 h after administration. Initially, there are fluctuations or changes in brightness or illumination, shapes are distorted, the colours are more intense and bright and constantly vary in pitch and intensity (Passie et al. 2008; Jones 2009; Sanders-Bush and Hazelwood 2011; O'Brian 2011). Auditory distortions are less common. At higher doses, synaesthesia may occur (perceiving a sensation in a different modality such as hearing colours). Distortions regarding the perception of time include time halting, stretching, repeating and ceasing to exist. The sense of self can change dramatically, even to depersonalisation. It feels as if the mind has left the body and as if there were a union of the self with the Universe. There are frequent religious, philosophical or mystical experiences. Psychological symptoms include multiple mood alterations, ranging from happy to sad. When the overall experience is perceived as enlightening or emotionally stimulating, it is referred to as a "good trip". Other times, the experience might be nightmarish, with fears of insanity or losing control, and anxiety. Such negative experiences are referred to as "bad trips". The cause of good trips versus bad trips is not known. The psychic experience generally lasts 8–12 h and is often followed by a pleasant "psychic numbness".

35.2.1.5 Clinical and Diagnostic Aspects

Tolerance to the psychological effects of lysergic acid diethylamide, but not the physiological effects, develops quickly (Blaho et al. 1997). In contrast to highly addictive drugs, such as cocaine and heroin, they do not produce physical dependence or withdrawal syndrome upon cessation of consumption. There is a clear and accurate memory of what happened during the hallucinogenic experience.

Intoxication

Patients come to have symptoms of sympathetic activation, perceptual changes and psychiatric symptoms (agitation, anxiety, panic, psychosis). There are also frequent "bad trips" that present with psychiatric symptoms (anxiety or significant panic reaction). Intoxications are occasionally accompanied by delirium (a separate diagnostic category). The elimination of the substance gradually improves the symptoms. There are no documented fatalities from LSD use, but fatal accidents and suicides have occurred during intoxication.

Hallucinogen Persisting Perception Disorder

Flashbacks are referred to as hallucinogen persisting perception disorder by the DSM-V when they cause significant distress. They are defined as "the transient recurrence of disturbances in perception that are reminiscent of those experienced during one or more earlier Hallucinogen Intoxications" (American Psychiatric Association 2013).

The most common phenomena are visual distortions, such as colour confusion, geometric hallucinations and trailing, but the content of the flashback may involve

any of the senses. It is not known what causes flashbacks. Theories include persisting damage to visual processing systems, dysfunction of inhibitory cortical interneurons, reverse tolerance, and that they comprise an atypical dissociative state (Garratt et al. 1993). Flashbacks may occur several days to several years after the antecedent use of lysergic acid diethylamide and have been reported with mescaline, phencyclidine and marijuana. Some users find these episodes pleasant and even refer to them as "free trips". For others they can be terrifying and recur frequently (hallucinogen persisting perception disorder). An antecedent good trip does not predict a good flashback. It is unclear what determines who will experience flashbacks and whether or not the experience will be pleasant (McGee 1984).

Flashbacks have reportedly been induced by a myriad of situations, including stress, exercise, pregnancy, sexual intercourse, dark environments, flashing lights, monotony, and use of other psychoactive drugs. It is estimated that anywhere from 15 % to 60 % of LSD users experience flashbacks. The flashback experience is often precipitated by psychiatric illness, as with the use of other drugs (Lerner et al. 2002). It is possible that the success of the medications listed above is related to the treatment of concurrent illness. Regardless of treatment, the frequency of flashbacks tends to decrease with time.

Persistent Psychosis Related to Mental Illness

Occasionally, LSD appears to precipitate a "persistent psychosis", characterised by visual hallucinations, mania, grandiosity, and religiosity. It is estimated to occur in 0.08–4.6 % of people who have used lysergic acid diethylamide (Meyerhoefer 2011).

Chronic effects include descriptions of permanent schizoid disorders, and subsequent or prior ingestion associated with LSD. Although the association between the occurrence of permanent psychosis and LSD is well established in various publications, it is not known precisely what the actual risk is. It seems that LSD would not be the direct cause of the development of permanent disorders, but LSD intake would act as a trigger of a pre-existing disease state (Passie et al. 2008; Jones 2009; O'Brian 2011; Sanders-Bush and Hazelwood 2011; Krebs and Johansen 2013).

Affective Disorders

While feelings of being overwhelmed, scared and afraid of losing control occur in a panic attack, lysergic acid diethylamide intoxication is further characterised by dramatic and persistent perceptual distortions. As with any altered mental state, the clinician should have a low threshold for suspecting delirium. Unlike delirium, there is no fluctuation level of consciousness with LSD intoxication. There is no specific pharmacological treatment for this disorder. When the patients stop consumption anxious-depressive syndrome may occur, requiring symptomatic treatment (Passie et al. 2008; Jones 2009; O'Brian 2011).

Somatic Complications

Although LSD is considered relatively safe compared with other drugs of abuse, there are case reports of respiratory failure, hyperthermia and coagulopathies

associated with massive doses. Early on, a relationship between lysergic acid diethylamide and chromosomal damage was suspected, but this has been consistently refuted and lysergic acid diethylamide does not appear to be teratogenic. LSD, however, does induce uterine contractions, which could disrupt pregnancy.

35.2.1.6 Therapeutic Aspects

The aim is to reduce consumption and achieve abstinence. Although initially is easy to stop consuming, because there is no physical dependence, it is more complex in the medium term. Often, bad trips facilitate abstinence or not wanting to repeat the experience. As in other drug addiction programmes, psychiatric and psychological support components are used.

There are no specific drugs for treating disorders caused by these substances. Psychotropic drugs will be used according to the patient's symptoms (benzodiazepines, antipsychotics, antidepressants). The "bad trip" generally does not require inpatient hospitalisation because of the limited time course and quick recovery. The patient should be placed in a quiet, non-stimulating environment and provided with continuous reassurance that his or her state of mind is drug-induced and will not result in permanent brain damage.

Given that most emergency rooms are chaotic and understaffed, this may not be a realistic option. Furthermore, the patient may be too disorganized or combative to be "talked down". When medications are needed, benzodiazepines are probably the best choice, as long as delirium has been ruled out. The use of neuroleptics should be reserved for instances where none of the aforementioned efforts have succeeded. High-potency (less anticholinergic) neuroleptics should be used because anticholinergics have been associated with paradoxical reactions, such as hypotension, and anticholinergic crises. The use of haloperidol and chlorpromazine carries a high potential risk of seizures.

Mescaline

Mescaline, or 3,4,5-trimethoxyphenylethylamine is a phenethylamine hallucinogen found in several species of North and South American cacti, including Peyote (*Lophophora williamsii)* and San Pedro. Mescaline was first isolated from peyote cacti in 1896 and was synthesised approximately 20 years later.

Natural peyote has a bitter taste. It is dried and chewed, soaked in water and drank or injected. The hallucinogenic dose is approximately 5 mg/kg (0.3–0.5 g). Each button contains about 50–100 mg of mescaline, and users typically ingest 3–8 buttons. Within the first 30 min, before the onset of psychological symptoms, users may experience nausea, vomiting, restlessness and headaches. By 1–2 h, however, these unpleasant physiological symptoms dissipate and the psychic phase, characterised by euphoria, sensory distortions, and feelings of confidence, begins. The entire experience lasts up to 14 h. As is the case with LSD and the other serotonergic hallucinogens, tolerance develops rapidly and physical dependence does not occur. Treatment of acute intoxication and adverse consequences, as with LSD and psilocybin, involves reassurance and use of benzodiazepines if necessary (Jones 2009).

Tryptamines

There are a number of non-controlled tryptamines that are used for their psychedelic properties. They have effects similar to the tryptamines already controlled such as psilocybin (found in *Psylocybes* mushrooms or "magic mushrooms") or dimethyltryptamine (DMT). Tryptamines can be synthesised, although they also exist in plants, fungi and animals.

Albert Hoffman isolated and then synthesised psilocybin. It was marketed by Sandoz laboratories under the trade name Indocybin® as a potential tool for psychotherapy in the 1960s. The mushrooms can be eaten fresh, dried, or brewed. They are usually ingested orally. Psilocybin is a prodrug that is converted in the body into the pharmacologically active compound psilocin by a dephosphorylation reaction. Typical doses of psilocybin range from 4 to 20 mg (40 μg/kg) corresponding to 1–2 g of dried mushrooms. Sympathomimetic symptoms occur at lower doses (3–5 mg), and psychological effects are elicited by doses above 8 mg. Psychological effects begin within 30 min of ingestion, peak at 2–3 h, and dissipate by 12 h (Passie et al. 2002). Psilocybin occasioned sustained experiences similar to spontaneously occurring mystical experiences. Only one third of "magic mushrooms" bought on the street actually contain psilocybin (many are simply store-bought mushrooms laced with phencyclidine) and there are many wild poisonous mushrooms. Adulteration and misidentification are the most common causes of serious adverse outcomes. As with the other serotonergic hallucinogens, tolerance develops quickly, but physical dependence does not occur (Griffiths et al. 2006, 2011).

Dextromethorphan

Dextromethorphan is the dextro isomer of levorphanol, a codeine derivative. It is a substance commonly used as a cough suppressant at doses between 15 and 30 mg orally every 6–8 h. It is marketed in single or in multicomponent medicines for the treatment of symptoms associated with the common cold or flu. In some countries dextromethorphan is used as an adjunct to morphine in the treatment of pain. It is a hallucinogen when administered orally at doses of 240–480 mg.

The hallucinogenic effects of dextromethorphan are due to its antagonistic action on NMDA glutamate receptors. It has no opioid activity.

Readily absorbed orally, it is metabolised to dextrorphan, which is the active ingredient in cough medicine, by cytochrome P-4502D6. Up to 5–10 % of Caucasians have a deficiency of this isoenzyme and therefore cannot metabolise dextromethorphan to dextrorphan (poor metabolisers). This drug is commonly used to determine the phenotype of said cytochrome. The elimination half-life is 1.5–4 h for dextromethorphan and somewhat higher for its major metabolite, dextrorphan, in extensive metabolisers. It is a minority use substance, commonly used as ketamine to provoke feelings of mind–body separation and pictures of so-called near-death experiences. Poisoning presents with light-headedness, fatigue, nausea and vomiting, and ataxia. Also described are euphoria, nystagmus, mydriasis or even coma and death, plus cases of psychosis, dystonia and serotonin syndrome. In the event of poisoning, supportive measures and symptomatic treatment are recommended (Abanades et al. 2004, 2007a, b).

Salvia divinorum

Salvinorin A is the psychoactive substance in the plant *Salvia divinorum*. It can induce dissociative effects and is a potent producer of visual and other hallucinatory experiences. Salvinorin A, appears to be the most potent naturally occurring hallucinogen. Its native habitat is the cloud forests in Mexico. It has been consumed for hundreds of years by local Mazatec shamans, who use it to facilitate visionary states of consciousness during spiritual healing sessions. It is also used in traditional medicine at lower doses as a diuretic to treat ailments including diarrhoea, anaemia, headaches and rheumatism.

In Canada, a national school survey in 2011 reported the widespread use of novel psychoactive substances (NPS) among tenth-grade students (aged 15–16), including *Salvia divinorum* (lifetime prevalence of 5.8 %), jimson weed, or *Datura* (2.6 %), a hallucinogenic plant. The general household survey for 2011 lists only *Salvia divinorum* (lifetime prevalence of 1.6 %) among NPS. According to the 2011 Eurobarometer survey (Gallup Organization 2011), Latvia is the country with the highest lifetime prevalence the use of *Salvia divinorum* in the European Union. In the USA the use of *Salvia divinorum* in youths (aged 17–18) has an annual prevalence of 5.9 % (United Nations Office on Drug and Crime Drug 2013).

Salvinorin A is present in the dried plant (about 0.18 %). It is a potent and selective kappa-opioid receptor agonist; in addition, it is a potent D2 receptor partial agonist, and it is likely that this action plays a significant role in its effects as well. *Salvia divinorum* is usually smoked and produces rapid and intense effects with a short action (15–30 min). Its effects include various psychedelic experiences, including past memories (such as revisiting places from childhood memory), merging objects and overlapping realities (such as the perception of being in several locations at the same time). In contrast to other drugs, its use often prompts dysphoria, i.e. feelings of sadness and depression, as well as fear. In addition, it may prompt a decreased heart rate, slurred speech, lack of coordination and possibly loss of consciousness.

Differing studies suggest no overall consensus so far with regard to the long-term effects of *Salvia* on mood. It is well-established that some kappa-opioid agonists can cause dysphoria in humans, and research using rats in forced-swim tests has been used to suggest that *Salvia* might have "depressive-like" effects.

Ayahuasca

Ayahuasca, also commonly called yagé, is a hallucinogenic brew of various psychoactive infusions or decoctions prepared with the *Banisteriopsis caapi* vine (which contains the beta-carboline alkaloids harmaline and harmine). It is mixed with the leaves from the genus *Psychotria* (*Psychotria viridis*) that contain dimethyltryptamine (DMT). DMT itself is not active orally because it is normally destroyed by deamination enzymes in the gut, but when the two plants are ingested together the beta-carboline alkaloids inhibit the deamination enzymes that ordinarily destroy DMT (monoamine oxidase, MAO). Ayahuasca is used largely as a religious sacrament. The psychedelic effects of ayahuasca include visual and auditory stimulation, the mixing of sensory modalities, and psychological

introspection that may lead to great elation, fear, or illumination. Its purgative properties are important, producing intense vomiting and occasional diarrhoea. In native or religious communities using ayahuasca, there is no evidence of psychological maladjustment, mental health deterioration or cognitive impairment (Bouso et al. 2012).

Ibogaine

Ibogaine is an indole alkaloid found in plants such as *Tabernanthe iboga*. The plant originates in Africa and is traditionally used in sacramental initiation ceremonies. Ibogaine is a hallucinogen at the 400-mg dose range. Ibogaine is a tryptamine that acts as an agonist (for the 5-HT2A receptor). In addition, it acts as an antagonist of the NMDA receptor set and an agonist for the kappa-opioid receptor. Ibogaine is metabolised in the human body by cytochrome P4502D6, and the major metabolite is noribogaine (12-hydroxyibogamine). Noribogaine is most potent as a serotonin reuptake inhibitor and acts as a moderate kappa-opioid receptor antagonist and weak mu-opioid receptor full agonist. In recent years, ibogaine has been studied, and even patented as a pharmacotherapy for opiate and other addictions, involving doses that range as high as 1,500 mg orally. There are no well controlled studies in humans assessing its efficacy at opiate detoxification. The ingested material is taken from the plant or pure powder (Brown 2013). Ibogaine can produce a QT interval prolongation and induce ventricular tachycardia after initial use. Fatalities following ibogaine ingestion are documented in the medical literature (Alper et al. 2012).

35.2.2 Dissociatives

Dissociatives include phencyclidine (PCP, angel dust), ketamine (Special K) and esketamine, and other recent derivatives that sometimes are classified in the novel psychoactive substances category (such as methoxetamine, methoxydine or 4-MeO-PCP, among others). Chemically, dissociatives are arylcyclohexylamine derivatives. These substances were developed as anaesthetics. Phencyclidine was quickly discarded because of a high frequency of postoperative delirium with hallucinations. It was classified as a dissociative anaesthetic because, in the anaesthetised state, the patient remains conscious with analgesia, staring gaze, flat facies and rigid muscles. The use of ketamine persists, especially in animals and humans, as an analgesic and anaesthetic.

35.2.2.1 Phencyclidine

Phencyclidine is rarely consumed in Europe, but is very common in the USA. Approximately 2.5 % of the US population reports having ever used phencyclidine. The proportion of users increases with age, from 0.3 % of 12- to 17-year-olds, to 1.3 % of 18- to 25-year-olds, to 2.9 % of those aged 26 years and older reporting ever having used phencyclidine. There appears to have been an increase among 12th graders in ever used (1.6–2.3 % over the past 3 years) (Johnston et al. 2013a).

Phencyclidine is injected intravenously, smoked, snorted or ingested orally. It is a substance that causes medical complications, resulting often in a more toxic effect than that of LSD. It is estimated that up to 3 % of deaths in drug users in the USA are due to phencyclidine.

Phencyclidine is an antagonist of NMDA glutamate receptors. It also activates the dopaminergic ventral tegmental area, the area starting in the reward pathway. There is tolerance to the effects, but not physical dependence. It tends to be used infrequently, although there is a small percentage of daily users. The elimination half-life is 21 h. At low doses (less than 5 mg) ataxia, dysarthria, blurred vision, nystagmus and weakness were produced. At higher doses (5–10 mg) hypertonia, hyperreflexia, hypertension, tachycardia, sweating, fever, vomiting, stereotyped movements and muscle stiffness appear. Often, aggressive and transient confusional episodes emerge (with psychomotor agitation, belligerence and impulsivity). Also, phencyclidine induces changes in perception, disorganised thinking and a feeling of unreality. At even higher doses, analgesia, amnesia and coma can occur.

The intoxication is a medical emergency because it can be severe and life-threatening. Hyperpyrexia, muscle stiffness, seizures, severe hypertension, intracerebral bleeding and respiratory depression can be observed. Patients go to the emergency room with high levels of hostility, aggressiveness, agitation, anxiety and self-injurious behaviour. It is the substance that produces more pictures of psychosis than any other. It is treated symptomatically with the administration of anxiolytics (diazepam) and antipsychotics (haloperidol) (O'Brian 2011).

35.2.2.2 Ketamine

Ketamine exists as two optical isomers, S and R-., the S-(+) isomer is more potent that the R(−) isomer. The S-isomer, or esketamine, has been recently marketed in some countries. Ketamine is used via an intramuscular or intravenous route as an analgesic and anaesthetic. Recently, ketamine has been used experimentally for the therapy of treatment-resistant depression (Aan Het Rot et al. 2012).

In the case of ketamine, in the UK, 1.8 % of 16- to 24-year-olds reported last-year ketamine use, with levels remaining stable between 2008 and 2012, although they increased from 0.8 % in 2006. Targeted surveys in nightlife settings report higher levels of lifetime prevalence, for example, in Danish clubbers 10 % had tried ketamine. Among UK respondents to an Internet survey who were identified as regular clubbers, 40 % reported last-year use of ketamine and 2 % last-year use of GHB (European Monitoring Centre for Drugs and Drug Addiction 2013a). In the United States the past-year use of ketamine appears to be relatively stable among 12th graders (1.5–1.7 % over the past 3 years) (Johnston et al. 2013a). In Canada, among tenth-grade students (aged 15–16) lifetime prevalence of ketamine use was 1.6 %. Given the strong decline in ketamine use in the United States since the beginning of the millennium, its use among tenth-grade students in Canada is now slightly higher than in the United States (1.2 % in 2011). In Australia, a small

decline occurred in the annual prevalence of ketamine use among the population aged 14 and above, from 0.3 % in 2004 to 0.2 % in 2010 (United Nations Office on Drug and Crime 2013).

Although the pharmaceutical presentation is injectable solution, it is transformed and crystallised in powder to consume. The illegal use of ketamine (Special K, Super K, kit-kat, K) has been increasing in recent years and is one of the so-called club drugs, drugs used at electronic music parties. Another type of consumption is related to the search for new sensations. Consumers also use ecstasy and gamma hydroxybutyrate (GHB). Like PCP, ketamine is an antagonist of the NMDA glutamate receptors. It is administered by injection intramuscular or intravenous), orally, by smoking and by inhalation. The elimination half-life of ketamine is 2–3 h. The effects are fast, short-lasting and dose-dependent, and can cause perceptual changes (from dissociation body sensation to near-death experiences) and psychopathological reactions similar to those of phencyclidine (Morgan and Curran 2012).

Appealing effects described by users include visual hallucinations and out-of-body experiences; undesirable effects include memory loss and decreased sociability. General central nervous system depressant effects include poor concentration and poor recollection similar to alcohol intoxication, which is not unexpected for an anaesthetic drug. Effects of ketamine include profound changes in consciousness and psychotomimetic effects, such as changes in body image (feeling that the body is made of wood, plastic, or rubber) and possible feelings of spiritual separation from the body, including out-of-body experiences. At low doses, users describe mild dissociative effects, distortion of time and space, and hallucinations. At large doses, users experience severe dissociation with intense detachment such that their perceptions seem to be located deep within their consciousness and reality is far off in the distance; this is called the "K-hole". The analgesic and dissociative effects may result in injury or even death.

Tolerance to the desired effects develops rapidly, resulting in reduced length of the subjective experience and requiring an increase in dose to maintain the expected effects. Users escalate the amount used to achieve the full hallucinogenic experience, up to seven times the original amount. Use of higher recreational doses can result in more adverse effects, especially physiological side effects. Use of very high doses can result in the onset of full anaesthetic effects, which may result in an overdose situation for a recreational user. Continued use of ketamine or phencyclidine, despite experiencing these consequences, constitutes addiction (using the phencyclidine use disorder criteria). Some people develop compulsive consumption, which is more reminiscent of the use of cocaine or psychostimulants.

The clinical symptoms of intoxication from ketamine are tachycardia, altered consciousness, disorganised speech and nystagmus. Treatment consists of supportive measures. Some ketamine users suffer urinary symptoms such as urinary frequency, urgency, dysuria and haematuria, which improve or disappear after cessation of use (Abanades et al. 2004, 2007a, b; O'Brian 2011).

35.2.3 Designer Drugs and "Legal Highs": MDMA and New Psychoactive Substances

35.2.3.1 Definitions

The emergence of new psychoactive substances that are not controlled under existing drug laws is not a new phenomenon. Over the last 20 years, a variety of terms and definitions have been used for new psychoactive substances that emerge on the market and are not under international control. The use of different terms to define the same substance can create confusion, because it can be found in different categories. Currently, the preferred term is new/novel psychoactive substances (NPS).

The emergence started in the 1970s with the so-called "designer drugs". They were defined as psychoactive substances produced from chemical precursors in a clandestine laboratory, which, by slight modification of the chemical structure, have been intentionally designed to mimic the properties of known psychoactive substances, and which are not under international control (Buchanan and Brown 1988). Over the past few years, the globalisation and the widespread use of the internet have allowed the unprecedented growth in both the number and availability of these substances. In the European Union (EU), 24 novel psychoactive substances were identified for the first time in 2009, 41 in 2010, 49 in 2011 and 73 in 2012 (European Monitoring Centre for Drugs and Drug Addiction 2013b).

"Designer drugs" have been defined by the International Narcotics Control Board as follows: "Substances that have been developed especially to avoid existing drug control measures and are manufactured by making a minor modification to the molecular structure of controlled substances, resulting in new substances with pharmacological effects similar to those of the controlled substances" (United Nations Office on Drug and Crime 2013). According to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and the European Police Office (Europol), designer drugs can be best defined as substances designed to mimic the effects of known drugs by slightly altering their chemical structure in order to circumvent existing controls.

More recently, "legal highs" has been used as an umbrella term for unregulated novel psychoactive substances, or products claiming to contain them, which are intended to mimic the effects of controlled drugs. The term includes a wide range of synthetic and/or plant-derived substances and products. These may be marketed as "legal highs" (emphasising "legality"), "herbal highs" (stressing the natural/plant origin), as well as "research chemicals" and "party pills"." Legal highs" are usually sold via the internet or in bricks and "head shops" or" smart shops". In most cases they are intentionally mislabelled with regard to their intended use (e.g. labelled as "not for human consumption", "plant food", "bath salts", "room odourisers", "incenses") and the active substances that they contain. This "legal highs" market can be distinguished from other drug markets by the speed at which suppliers circumvent drug controls by offering new alternatives to restricted products (Deluca et al. 2012).

Currently in the European Union a new psychoactive substance is defined as a new narcotic drug or a new psychotropic drug in pure form or in a preparation that has not been scheduled under:

1. The 1961 United Nations Single Convention on Narcotic Drugs, and that may pose a threat to public health comparable to the substances listed in Schedule I, II or IV; or,
2. The 1971 United Nations Convention on Psychotropic Substances, and that may pose a threat to public health comparable to the substances listed in Schedules I, II, III or IV. In this context, the term "new" is not intended to refer to newly invented, but rather to a "'newly available" or a "newly misused" substance. In practice, most "new" drugs were first described in the scientific and patent literature many years ago as part of legitimate research and development, but have not been widely available or used (Sedefov et al. 2013). Novel psychoactive substances are defined by the United Nations Office for Drug and Crime as "substances of abuse, either in a pure form or a preparation, that are not controlled by the 1961 Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, but which may pose a public health threat".

35.2.3.2 Origin and Synthesis

As mentioned above, the term "designer drug" was coined in the 1980s. It originally referred to various synthetic opioids, mostly based on modifications of fentanyl (alfa-methyl-fentanyl) and pethidine. The term entered widespread use when 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") experienced a boom in the mid-1980s, first in the USA, followed by Europe in the 1990s and then other parts of the world. Another term that emerged in the late 1990s and early 2000s is "research chemicals" (RC). The term was coined by some marketers of designer drugs, specifically, psychedelic drugs of the tryptamine and phenethylamine families. The idea was that by selling the chemicals for so-called "scientific research" rather than for human consumption (they included the advice "not for human use or consumption"), the drug laws could be circumvented. The same strategy was behind the marketing of some of the cathinone-related substances as "bath salts" not intended for human consumption (Camí and Farré 2003).

Substances sold as "legal highs" are mainly manufactured in chemical laboratories in Asia, according to the International Narcotics Control Board and the Europol, although some manufacture also takes place in Europe, the Americas and other regions. They are legally imported, either as chemicals or as packaged products. The "legal highs" market is characterised by the speed with which suppliers circumvent drug controls by offering new alternatives to restricted products and advertise them with aggressive and sophisticated marketing strategies (as air fresheners, herbal incenses, bath salts, plant fertilisers, collectors' items etc. (European Monitoring Centre for Drugs and Drug Addiction 2012).

New psychoactive substances can be classified as shown in Table 35.2.

Phenethylamine, including MDMA, and tryptamine derivatives are shown in Table 35.1 above.

Table 35.2 Classification of substances categorised as novel psychoactive substances (NPS) based on the systems used by United Nations Office on Drugs and Crime (UNODC) and European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Some of the substances of each class are included as examples

Group	Substances
Synthetic cannabinoids	JWH-018
	JWH-073
	JWH-200
	JWH-250
	AM-694
	CP 47,497
	Cannabicyclohexanol
	CP 55,940
	HU-210
	THC-O-acetate
Synthetic cathinones	Cathinone
	Methcathinone (ephedrone)
	Methylmethcathinone (mephedrone)
	Methylenedioxypyrovalerone (MDPV)
	Pyrovalerone
	Naphyrone (naphthylpyrovalerone, NRG-1)
	Ethylone (see Table 35.1, entactogens)
	Methylone (see Table 35.1, entactogens)
	Butylone (see Table 35.1, entactogens)
Phenethylamines	See Table 35.1
	Paramethoxymethamphetamine (PMMA)
	2,5-dimethoxy-4-iodophenethylamine (2C-I)
	2,5-dimethoxy-4-methyl-phenethylamine (2C-D)
	2,5-dimethoxy-4-iodoamphetamine (DOI)
	2,5-dimethoxy-4-bromo-phenethylamine (2-CB)
	4-methylthioamfetamine (4-MTA)
Piperazines	1-benzylpiperazine (BZP)
	1-(3,4-methylenedioxybenzyl) piperazine (MDBP)
	1-(3-chlorophenyl) piperazine (mCPP)
	1-(3-trifluoromethylphenyl)piperazine(TFMPP)
	1-(4-methoxyphenyl)piperazine (MeOPP)

(*continued*)

Table 35.2 (continued)

Group	Substances
Ketamine and phencyclidine-type substances	See Table 35.1
	Ketamine
	N-ethylnorketamine
	3-methoxy-phencyclidine (3-MeO-PCP)
	4-methoxy-phencyclidine (4-MeO-PCP)
	Eticyclidine (PCE, CI-400, *N*-ethyl-1-phenylcyclohexylamine)
	2-(3-methoxyphenyl-2-(ethylamino)cyclohexanone) (methoxetamine)
	Rolicyclidine (PCPy; 1-(1-phenylcyclohexyl)pyrrolidine)
	Tenocyclidine (TCP; 1-(1-(2-thienyl)cyclohexyl)piperidine)
	2-(3-methoxyphenyl-2-(ethylamino)cyclohexane) (3-MeO-PCE)
Tryptamines	See Table 35.1
Plant-based psychoactive substances	Kratom (*Mitragyna speciosa*)
	Salvia divinorum
	Khat (*Catha edulis*)
Other	
Aminoindanes	2-Aminoindane (2-AI)
	5,6-Methylenedioxy-*N*-methyl-2-aminoindane (MDMAI)
	5,6-Methylenedioxy-2-aminoindane (MDAI)
	5-Methoxy-6-methyl-2-aminoindane (MMAI)
Benzofuranes	5-(2-Aminopropyl)-2,3-dihydrobenzofuran (5-APDB, 3-Desoxy-MDA, EMA-4)
	6-(2-Aminopropyl)-2,3-dihydrobenzofuran (6-APDB, 4-Desoxy-MDA, EMA-3)
Piperidines	Pipradrol
	Desoxypipradrol (2-diphenylmethylpiperidine, 2-DPMP)
Synthetic cocaine	Dimethocaine
	4-fluorotropacocaine
Medicines	Phenazepam
	Etizolam
	Ethylphenidate
	Phenibut
	4-methylphendimetrazine

35.2.3.3 Epidemiology and Pattern of Consumption

During 2012, 73 NPS were notified by the European Member States for the first time through the EU Early Warning System. Reflecting consumer demand for cannabis-like products, 30 of these substances were synthetic cannabinoid receptor agonists. Nineteen compounds did not conform to the readily recognised chemical groups (including plants and medicines), while 14 new substituted phenethylamines were reported, the highest number since 2005 (European Monitoring Centre for

Drugs and Drug Addiction 2013b). As the internet is an important marketplace for NPS, the EMCDDA undertakes a regular snapshot exercise to monitor the number of online shops offering products to European consumers. This number of shops continues to grow, with 693 online shops identified in January 2012.

The use of NPS has grown rapidly over the past decade, in contrast to the prevalence of the use of internationally controlled drugs, which generally seems to have stabilised in the same time period. Producing and marketing such substances holds the promise of high profits without penalty. When brought under control in one country, production and/or the distribution centres of these substances are shifted to another country so that the sales, often conducted via the internet, can continue.

In other cases, the substances are modified slightly so that they are not covered by the respective country's legislation. The number of NPS reported by Member States to the United Nations Office on Drugs and Crime (UNODC) rose from 166 at the end of 2009 to 251 by mid-2012. This exceeds the total number of psychoactive substances currently controlled by the international drug conventions (234 substances) (United Nations Office on Drug and Crime 2013).

Well-known examples of NPS include substances such as synthetic cannabinoids contained in various herbal mixtures, piperazines, products sold as "bath salts" (i.e. cathinone-type substances, such as mephedrone and methylenedioxypyrovalerone [MDPV]) and various phenethylamines. Ketamine was among the first NPS to appear. Its abuse was first recognised in North America at the beginning of the 1980s. It became a noticeable phenomenon in Europe in the 1990s, before spreading extensively throughout Asia and, to a lesser extent, throughout South America and Southern Africa. NPS belonging to the phenethylamine family appeared on the market in the 1990s and substances belonging to the piperazine family at the beginning of the 2000s. From 2004 onwards, synthetic cannabinoids, such as Spice, appeared on the market, followed by synthetic cathinones and other emerging groups of NPS.

According to the Eurobarometer, 5 % of young people reported having used these NPS in the past (Gallup Organization 2011). The national survey on drug use in students aged 14–18 years in 2010, conducted by the Spanish Drug Observatory (OED), assessed the use of ketamine, Spice drugs, piperazines, mephedrone, nexus (2-CB), methamphetamine, magic mushrooms, "research chemicals" and other LH. Reported prevalence of use was 3.5 %, 2.5 % and 0.5 % for lifetime, last year and last month respectively for any of these substances (Clinical Committee Report 2011).

The lifetime prevalence of legal substances that imitate the effects of illicit drugs rises with age, from 3.6 % among the European Union population aged 15–18 to 5.6 % among those aged 19–21 and 22–24. The lifetime prevalence for the use of legal substances that imitate the effects of illicit drugs in individual European Union countries ranged from 0.3 % in Malta to more than 16 % in Ireland. Levels above the European Union average (4.8 %) have been reported—in descending order—from Ireland, Poland, Latvia and the UK, followed by Luxembourg, Slovenia, Estonia, Portugal, Lithuania, France and Spain (United Nations Office on Drug and Crime 2013).

MDMA (Ecstasy) and Derivatives

The consumption of ecstasy is associated with attending electronic dance music events or raves. It is estimated that 1.8 million young adults used ecstasy in the last year, with national estimates ranging from under 0.1 % to 3.1 %. Consumption of the drug typically peaked in the early to mid-2000s, before declining. Between 2006 and 2011, most countries have reported stable or declining trends in ecstasy use. With the exception of Poland, this decline continues to be seen in data from countries reporting surveys since 2010. Few users entered treatment for problems relating to ecstasy in 2011: ecstasy was mentioned as the primary drug by less than 1 % (around 600 clients) of reported first-time treatment entrants in Europe. In young adults aged between 15 and 24, the (lifetime) prevalence in Europe of ecstasy use is between 0.4 % and 16.6 %, with the higher rates seen in the Czech Republic (European Monitoring Centre for Drugs and Drug Addiction 2013b).

In the United States the lifetime prevalence of ecstasy (MDMA) use in students in 12th grade was between 7.2 % and 8 % over the past 3 years. For amphetamines it was 11.1–12.2 %, and for methamphetamines 1.7–2.3 % (Johnston et al. 2013a).

Cathinones

There are signs that synthetic cathinones, including mephedrone, may have carved a space in the illicit stimulants market in some countries. At present, however, only the UK has repeat surveys that include these drugs. In the most recent data, 1.1 % of adults (16–59) in England and Wales reported using mephedrone in the last year, making it the fourth most commonly used illicit drug. Among 16- to 24-year-olds, last-year prevalence was the same as that of ecstasy (3.3 %), the third most prevalent drug among this age group. A decrease in levels of use, however, was noted for all groups compared with the 2010/2011 survey.

More generally, mephedrone-related mortality and morbidity continue to be reported in Europe, although at relatively low levels. Some countries also report the injection of mephedrone, MDPV and other synthetic cathinones among groups of problem drug users and drug treatment clients (Hungary, Austria, Romania, UK) (European Monitoring Centre for Drugs and Drug Addiction 2013b).

In the USA data on changes in the prevalence of the use of MDPV are not available. However, data show that the number of calls to poison control centres concerning “bath salts” (often linked to MDPV) rose from 304 in 2010 to 6,134 in 2011, a 20-fold increase in 1 year (United Nations Office on Drug and Crime 2013).

Piperazines

The British Crime Survey found in 2011 that the annual prevalence of BZP was 0.1 %. The Mixmag Global Drug Survey, in 2011, reported a lifetime prevalence of 17.2 % and last-year prevalence of 5 % and a prevalence in the last month of 0.5 % (United Nations Office on Drug and Crime 2013). In New Zealand, the market for NPS has been associated with piperazines. The national household survey there revealed that 5.6 % of the population aged 15–64 had used BZP in the past year (United Nations Office on Drug and Crime 2013).

35.2.3.4 Pharmacological Proprieties and Consequences of the Use of MDMA (Ecstasy)

The 3,4 methylenedioxymethamphetamine (MDMA) is a ring-substituted amphetamine that is structurally similar to methamphetamine and mescaline. MDMA has become widely known as "ecstasy" (shortened to "E", "X", or "XTC"). MDMA acts as a potent releaser and/or reuptake inhibitor of presynaptic serotonin (5-HT), dopamine (DA) and norepinephrine (NE). These actions result from the interaction of MDMA with the membrane transporters involved in neurotransmitter reuptake and vesicular storage systems. Globally, this results in the increased activation of postsynaptic receptors. In comparison to methamphetamine, MDMA is more potent and active on serotonergic neurons. MDMA is also a mild inhibitor of monoamine oxidase (MAO) and also has some direct action in several types of receptors including the 5-HT2 receptor, the M1 muscarinic receptor, the 2-adrenergic receptor and the histamine H1 receptor. MDMA inhibits the activity of the rate-limiting enzymes of serotonin synthesis (tryptophan hydroxylase), decreasing the formation of serotonin (de la Torre et al. 2013).

Ecstasy is presented for use as tablets/pills, capsules or powder (ice). It is usually taken orally, but some users snort the contents. The MDMA content of pills or tablets varies widely between regions and different brands of pills, and fluctuates. Pills may contain other active substances meant to stimulate in a way similar to MDMA, such as amphetamine, mephedrone, methamphetamine, ephedrine or caffeine. In some cases, tablets sold as ecstasy do not even contain any MDMA.

In general, users begin reporting subjective effects within 30–60 min of consumption, a peak appears at about 75–120 min, reaching a plateau that lasts about 3.5 h. This is followed by a comedown feeling of a few hours. The usual dose is 50–125 mg with additional doses throughout the recreational session. The most frequent effects after MDMA administration are euphoria, well-being, happiness, stimulation, increased energy, extroversion, feeling close to others, increased empathy, increased sociability, enhanced mood, mild perceptual disturbances, somatic symptoms related to the cardiovascular (increase in blood pressure and heart rate) and autonomic effects (dry mouth, sweating, tremor, mydriasis tremor, jaw clenching and restlessness), and moderate derealisation, but not hallucinations. Some of the effects differ from those elicited by classical amphetamines (e.g. feeling close to others, increased empathy, increased sociability) are collectively termed "entactogenic" and MDMA is considered the prototypical drug to produce such effects (de la Torre et al. 2013; Farré et al. 2004, 2007).

The MDMA-induced acute toxic effects occur in relation to its pharmacological actions. Signs of mild toxicity include nausea, vomiting, restlessness, tremor, hyperreflexia, irritability, pallor, bruxism, trismus and palpitations. Moderate intoxication signs include hyperactivity, aggressive behaviour, panic attacks, psychosis, confusion, muscle tension, tachycardia, arterial hypertension, and an increase in body temperature. Severe intoxication can include delirium, coma, seizures, hypotension, tachydysrhythmias, hyperthermia (>40 °C), and renal failure associated with rhabdomyolysis. A serotonin syndrome (increased muscle rigidity, hyperreflexia, and hyperthermia). Intracranial haemorrhage has been described.

Heat stroke is a severe complication that can cause death; it includes hyperthermia, rhabdomyolysis, myoglobinuria, disseminated intravascular coagulation and renal failure. Fulminant hepatitis and hepatic necrosis have been reported. Hyponatraemia is an uncommon complication associated with inappropriate antidiuretic hormone (SIADH) secretion and excessive water intake. Its chronic use is linked to a progressive neurodegeneration of the serotonergic neurotransmission system (de la Torre et al. 2013; Cuyas et al. 2011).

Two main pathways are involved in MDMA metabolic clearance:

1. *O*-demethylation partially regulated by CYP2D6 followed by catechol-*O*-methyltransferase (COMT)-catalysed methylation (HMMA) and/or glucuronide/sulphate conjugation; and
2. *N*-dealkylation leading to 3,4-methylenedioxyamphetanmine (MDA), further subject to similar metabolic reactions to MDMA (*O*-demethylenation and *O*-methylation). MDMA metabolic clearance accounts for about 75 % of plasma clearance and 30 % of its metabolism is regulated by CYP2D6 (de la Torre et al. 2005; Segura et al. 2005). In addition, MDMA is a competitive inhibitor of CYP2D6; after a single dose most hepatic CYP2D6 are inactivated within 2 h, returning to a basal level of CYP2D6 activity after at least 10 days. Other isoenzymes of cytochrome P450 and a relevant contribution of renal excretion play part in their clearance.

Globally, the clinical relevance of the CYP2D6 polymorphism (de la Torre et al. 2004, 2005) is lower than that predicted by in vitro studies (de la Torre et al. 2012; Yubero-Lahoz et al. 2011, 2012).

In addition, there is some evidence that MDMA produces in the mid- to long-term selective long-lasting serotonergic neurotoxicity in animal models when administered at relatively high doses and/or after repeated administration.

Unique low doses or repeated low doses separated by large intervals did not seem neurotoxic. It has been proposed that MDMA induces a number of serotonin neuroadaptations and anatomical alterations (e.g. axotomy of serotonergic neurons). Complementary or alternative to this view of MDMA-induced neurotoxicity, there is new evidence showing that MDMA causes substantial regulatory changes in the expression of serotonergic markers, including the serotonin transporter. The direct extrapolation of these results from animal to human is difficult (de la Torre and Farré 2004; Green et al. 2012).

In humans, ligand-binding imaging studies have reported decreased 5-HTT binding throughout the cerebral cortices and the hippocampus in Ecstasy users compared with healthy controls. Furthermore, these studies have shown that decreased 5-HTT binding is associated with lower memory performance in Ecstasy users. Although some studies have observed MDMA abstinence-related recovery of 5-HTT availability in the mid-brain and thalamus there are no data on 5-HTT recovery in the cortex, and post-mortem evidence indicates that cortical 5-HTT protein reductions can be more robust and durable than indicated by neuroimaging studies. Overall, these findings are suggestive of MDMA-induced neurotoxicity, which primarily affects the serotonin system and is linked to cognitive alterations (e.g. memory dysfunction) and a higher prevalence of

psychopathology (e.g. mood disorders) among Ecstasy users (de la Torre and Farré 2004; de la Torre et al. 2013; De Sola Llopis et al. 2008; Pardo-Lozano et al. 2012).

The therapeutic use of MDMA is under investigation. Few recent randomised, controlled trials of MDMA-assisted psychotherapy for post-traumatic stress disorder have been published showing some therapeutic efficacy (Mithoefer et al. 2013). MDMA can induce abuse, but it is not clear and in some cases drug dependence occurs, but not drug withdrawal. Users reported tolerance to its desired effects, and tend to cease consumption spontaneously. MDMA can cause intoxication, in this case the DSM-V diagnostic criteria for stimulants can be applied (American Psychiatric 2013). There are no specific drugs for treating disorders caused by MDMA. Psychotropic drugs will be used according to the patient's symptoms (benzodiazepines, hypnotics, antipsychotics, antidepressants). As in the other drug addiction programmes, psychiatric and psychological support are used.

35.2.3.5 Pharmacological Proprieties and Consequences of the Use of NPS

Synthetic Cannabinoids

The most widely used NPS are currently the synthetic cannabinoids, often mixed with various herbal mixtures and sold under the brand name Spice or other names. Initially, the most widespread synthetic cannabinoid was JWH-018. After it was prohibited in some countries in 2010, it was immediately replaced by other, similar compounds, such as JWH-073. Although the various synthetic cannabinoids differ, they tend to be more potent than the tetrahydrocannabinols (THC) contained in the natural cannabis plant. Similar to cannabis, these substances tend to elevate the mood, aid relaxation and alter perceptions (United Nations Office on Drug and Crime 2013; Mustata et al. 2009). Cannabinoids are fully described in other chapter.

Tryptamines

Some tryptamines have been associated with the emergence of NPS. Their main properties can be found in the hallucinogenics part of this chapter.

Phenethylamines

Phenethylamines include a large series of compounds that range from amphetamines or entactogens, such as MDMA to hallucinogens (see the part of this chapter on hallucinogens). A large number of non-controlled phenethylamines also fall into the category of NPS. However, the main phenethylamines on the illicit markets are already under international control, including amphetamine, methamphetamine and methylphenidate, as well as MDMA ("ecstasy") and mescaline. NPS phenethylamines appeared on the market after a shortage of ecstasy that occurs between 2009 and 2010; major substitutes were other amphetamines, mCPP and, above all, mephedrone.

They are presented in the form of pills, capsules or a powder, which users can swallow, snort or inject, producing similar effects to MDMA, amphetamines and hallucinogens. Amphetamines are chemically phenylethylamine derivatives, and

their structure exhibits similarity to various endogenous neurotransmitters (norepinephrine, dopamine and serotonin) and hallucinogens like mescaline.

The effects of phenethylamines depend on its selectivity on dopaminergic, serotonergic and noradrenergic neurons. They release these neurotransmitters and in addition inhibit its re-uptake interacting with the membrane transporters.

Those with psychostimulant effects are more selective for dopamine and norepinephrine transmission, the hallucinogenic derivatives have more effects on serotonin transmission. It is important to say that hallucinogenic derivatives produce those actions even at low doses and are not usually psychostimulants.

Some derivatives with actions like MDMA can produce entactogenic effects, a greater desire for contact with others, greater empathy, love and emotional closeness to others. At low doses, phenethylamines increase alertness, give energy to fatigued individuals and increase endurance. They also tend to have some anorectic properties as they produce sympathetic nervous system stimulation with increased pupillary diameter (mydriasis), which can cause blurred vision and increased sensitivity to light, dry mouth, sweating, tremor, tension jaw (lockjaw), chewing movements or grinding of teeth (bruxism) and a slightly increasing body temperature together with increased blood pressure and heart rate (palpitations or tachycardia). At higher doses, phenethylamines induce euphoria, stronger feelings of self-esteem (including diminished fear, anxiety and insecurity), but can also increase blood pressure, raise body temperature, increase the heart rate, cause hallucinations and lead to death due to stroke, cardiac arrest and brain damage (starting with memory loss). The use of phenethylamines can entail various forms of drug-related psychosis and paranoia. The more psychedelic phenethylamines tend to bring about the intensification of bodily senses (hearing, touch, smell, vision, taste) and thus also have some aphrodisiacal effects. They also create various hallucinogenic effects even at lower doses, entailing various mental, auditory and visual distortions. The human pharmacokinetics of the majority of phenethylamines are unknown (Caudevilla-Galigo et al. 2012).

Cathinones

Currently, the most problematic group of NPS from the perspective of public health and safety seems to be the synthetic cathinones, such as mephedrone (4-(methylmethcathinone, 4-MMC, 4-methylephedrone) or methylenedioxypyrovalerone (MDPV). Cathinones are derivatives of cathinone, which is found in the khat plant *(Catha edulis)*, although most are synthetically manufactured. Mephedrone and other cathinones can come in the form of capsules, tablets or white powder that users may swallow, snort, inject, smoke or use rectally, producing similar effects to MDMA, amphetamines and cocaine.

A number of cathinones are already under international control, including cathine, cathinone and methcathinone, as well as amfepramone and pyrovalerone. The most widely used, non-controlled cathinones at the international level include mephedrone (often known in the market as “m-cat”, “meph”, “drone” or “meow”), methylone (“explosion” or “top cat”) and MDPV.

Mephedrone and the cathinones are expected to act as a central nervous system stimulant by promoting the release of monoamine neurotransmitters and likely inhibiting their reuptake. Both amphetamines and cathinones bind to norepinephrine, dopamine and serotonin transporters, each of them differing from each other by its relative binding potency. In particular, the presence of the ring substituent on the phenethylamine core modifies the pharmacological properties by giving the compound some MDMA-like effects, whereas amphetamines and cathinone derivatives without ring substituents exert mostly stimulant effects (European Monitoring Centre for Drugs and Drug Addiction 2012). The human pharmacology, including pharmacokinetics of the majority of new cathinones are unknown (Schifano et al. 2011).

The most common routes for recreational use include insufflation (snorting) and oral ingestion. Because of its solubility in water, mephedrone is reportedly used for rectal administration (dissolved in an enema or within gelatine capsules) as well as injecting intravenously. Insufflation is likely to be the most common modality. When snorted, mephedrone elicits its effects within a few minutes, with the peak being reached in <30 min followed by a rapid comedown. According to online users' advice, mephedrone dosage for snorting may range between 25 and 75 mg, with the lower threshold being at 5–15 mg, and with a level in excess of 90 mg to be considered a high dosage.

Mephedrone effects have been variously compared by users with those of cocaine, amphetamine and MDMA. Self-reported subjective effects may include: intense stimulation and alertness, euphoria, empathy/feelings of closeness, sociability and talkativeness, intensification of sensory experiences, moderate sexual arousal and perceptual distortions (reported with higher dosages only). Some 56 % of those who had used mephedrone may complain of at least one unwanted effect associated with its use. These may include: loss of appetite, dry mouth, nausea, vomiting, tremors, tense jaws, trismus, bruxism, mild muscle clenching, stiff neck/shoulders, headache (very common), dizziness/light headedness, tinnitus, seizures, nystagmus, pupil dilation, blurred vision, numbness of tactile sensitivity; anxiety, agitation, confusion, dysphoria, irritability, aggression, depression, lack of motivation and anhedonia; time distortions, long-lasting hallucinations, paranoid delusions, short-term psychosis, short-term mania, insomnia and nightmares; impaired short-term memory, poor concentration and mental fatigue; tachycardia, elevated blood pressure, respiratory difficulties, chest pain and vasoconstriction (Schifano et al. 2011; Hill and Thomas 2011; Wood et al. 2011).

The use of ephedrone (methylcathinone) has recently been associated with symptoms similar to those seen in patients with Parkinson's disease (manganism) owing to the compound manganese dioxide, which is a by-product of synthesis with permanganate (De Bie et al. 2007).

The use of MDPV was, in a number of cases, associated with highly bizarre behaviour, including a number of suicides, deaths associated with MDPV delirium and highly violent homicides (Murray et al. 2012).

Piperazines

The basic piperazine was first introduced into medicine in 1953, for its anthelmintic properties. The piperazines can be classified into two groups:

- Benzylpiperazines including 1-benzylpiperazine (BZP), and its analogue 1- (3,4-metilenodioxibenzil) piperazine (MDBP).
- The phenylpiperazines, such as 1-(3-chlorophenyl) piperazine (MCCP), 1-(3-trifluoromethylphenyl) piperazine (TFMPP), 1-(4-methoxyphenyl) piperazine (MeOPP), 1-(4-chlorophenyl) piperazine (pCPP) and 1-(*o*-methoxyphenyl) piperazine (WOFP).

BZP has been studied as an anthelmintic, but was never commercialised, unlike piperazine. The mCPP is an active metabolite of trazodone and nefazodone, both with antidepressant properties. It is used in psychopharmacological research as central serotonergic system challenge. Generically, they are known as "herbal highs", "herbal tonics", "herbal ecstasy" or "party pills". They are generally taken orally and are presented in the form of tablets or capsules. The BZP capsules contain 50 to 200 mg. The mCPP was introduced onto the market as a legal alternative to ecstasy in times of shortages. Often, the mCPP is sold as ecstasy or, in some tablets, mixed with MDMA. In fact, users are often unable to distinguish the effects of BZP from those of D-amphetamine; they report alertness, mood escalation, euphoria and a general feeling of well-being. BZP was initially legally marketed in some countries (notably New Zealand) as an alternative to methamphetamine. If combined with TFMPP, effects similar to those of MDMA ("ecstasy") are produced. Thus, BZP/TFMPP combinations have been widely used on the club and rave scene in many countries. These substances have been shown to have a mixed mechanism of action, acting on both the serotonin and the dopamine receptor systems, much like MDMA, thus showing entactogenic properties. In contrast to BZP, TFMPP is rarely used on its own. Street names of BZP include "Jax" and "Flying Angel". Tablets often contain various types of piperazines (MCCP mixtures, TFMMP, OMPP and/or pCPP). They can be found for sale on the internet, as essentially unrestricted derivatives.

Adverse effects of BZP include repetitive thought patterns, increased heart rate, hypertension, dilation of pupils, nausea, flushing, slight urinary incontinence, chest pain, hallucinations, confusion, acute psychosis, respiratory failure, renal toxicity and seizures. BZP produces toxic effects similar to those of amphetamines and other sympathomimetics. Fatal intoxications have been described (Hill and Thomas 2011; Schep et al. 2011).

Phencyclidine Derivatives

Some new phencyclidine and ketamine derivatives are considered NPS. Their main characteristics are explained in other parts of this chapter.

Plant-Based New Psychoactive Substances: Kratom

Kratom (*Mitragyma speciosa*) has been used in traditional Thai medicine as an antidiarrhoeal and it has been investigated for the treatment of opioid dependence. The cultivation and use of kratom is mostly linked to South-East Asia. However, it is also widely used recreationally, leading to its prohibition in Thailand as well as in

other countries, including Malaysia, Myanmar and Australia. There are 40 compounds in *M. speciosa* leaves, including many alkaloids such as mitragynine (thought to be the primary active constituent), mitraphylline, and 7-hydroxymitragynine (probably the most likely candidate for the primary active chemical in the plant). Kratom behaves as a mu-opioid receptor agonist like morphine, but also acts as a calcium channel blocker, and reduces NMDA-induced current. Kratom is a stimulant at low doses and a sedative at high doses. At low doses, it tends to increase physical energy and alertness and increases the ability to do monotonous physical work. At higher doses, it helps to reduce physical and emotional pain and tends to generate a feeling of well-being before eventually developing its sedative properties, creating a mixed state of wakefulness and dreaming. Withdrawal symptoms for chronic users of kratom may include muscle aches, irritability, crying, runny nose, diarrhoea and muscle jerking (Prozialeck et al. 2012).

35.2.3.6 Clinical and Diagnostic Aspects

Novel psychoactive substances can induce substance use disorder, intoxication and in some cases withdrawal syndrome (for those with psychostimulant properties). Depending on the substance and pharmacological effects, the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V) criteria for hallucinogens or stimulants can be applied (American Psychiatric 2013).

The therapeutic aim in these cases is to reduce consumption and achieve abstinence. In some cases of NPS use cessation can be easy because there is no physical dependence; in other cases (with a more psychostimulant profile) some symptoms of withdrawal syndrome can be observed. There are no specific drugs for treating disorders caused by these substances. Psychotropic drugs will be used according to the patient's symptoms (benzodiazepines, hypnotics, antipsychotics, antidepressants). As in the other drug addiction programmes psychiatric and psychological support components are used.

In the case of MDMA use disorder patients with dependence and persistent severity criteria were observed. In many cases it may be useful treat with pharmacological and psychological therapy.

It is very important to carry out a psychiatric evaluation by a specialist to diagnose a substance use disorder, and evaluate the comorbidity of psychiatric illnesses. In many cases early pharmacological treatment is necessary. It is important to be aware of cases of poisoning by NPS, as the pharmacodynamics are not yet known. It is recommended that samples are stored for study. To conclude, the emergence of new psychoactive substances as drugs of abuse is a serious problem which impacts global public health.

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Inhalant Addiction

36

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Contents

Abstract

Inhalants are a special class of drugs that require particular attention from health and social welfare experts and policy makers. They are substances of abuse not included in the International Regulations. They are also less frequently targets for health and social interventions as well as for research funding. Inhalants are

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the only drugs of abuse defined by the route of administration rather than by their attributes, specifically by similar mechanisms of action or common pharmacological effects. They include a broad group of substances with different uses, short and long-term negative effects, and consequences. These products have legal uses in industry and households and are therefore readily available. Inhalants are used by young students and populations with special needs, mainly children and adolescents from poor sectors of society, workers who use solvents for their everyday work (such as varnishers, house painters, and anesthetists), and heavy drug users, especially when they lack access to other substances. The short-term effects of inhalants are similar to alcohol and other central nervous system depressants and can produce impaired motor coordination, emotional liability, and speaking difficulties. Chronic effects include neurotoxicity, cognitive impairment, headaches, diminished sensorial abilities (loss of vision, audition, and coordination), and an increase in mental disorders and sleep disturbances. Inhalant use prevention involves different strategies, including education, skill building, environmental changes, and policy development. There is little research on evidence-based treatment for inhalant addiction. However, treatment should include supportive psychotherapy, family and psychosocial interventions, general health care proper nutrition, and vitamins or nutritional supplements. The long-term outcome of inhalant addiction is usually progressive neurocognitive deterioration with multiple medical complications.

36.1 Introduction

Inhalants are a special group of substances with varied effects, differences in use patterns and populations affected, and with special needs for prevention, treatment and policy formulations. This chapter focuses on this issue; it is divided in 6 sections, beginning with a general overview of the substances and definitions. This is followed by a description of prevalence, the groups of affected population and use patterns in different regions of the world. Particular attention is paid to use among groups with special needs, to their effects and consequences; the social determinants that underlie the problem and opportunities for solution are also addressed. These sections are followed by a brief overview of the evidence for prevention and treatment. The chapter ends with a discussion on policies to address the problem.

36.2 Definition and Classification

A working definition proposed by Balster and colleagues states that:

> Abused inhalants contain volatile substances that are self-administered as gases or vapors to induce a psychoactive or mind-altering effect. These volatile substances are available in legal, relatively inexpensive and common household products, which can be gases, liquids, aerosols or, in some cases, solids. (Balster et al. 2009)

NIDA's definition (2012) includes the main issues that characterize this varied group of substances and their effects: the intentionality of their use, due to the chemicals' mind-altering effects; the nature of the short-term effects (most of them produce a rapid high that resembles in some aspects alcohol intoxication); the effects when sufficient amounts are inhaled, as nearly all solvents and gases produce a loss of sensation and even unconsciousness; the long-term irreversible effects that can include hearing loss, limb spasms, and bone marrow and brain damage; and lastly, the risk of death when sniffing high concentrations of inhalants, which may result in death from heart failure hypothermia or suffocation.

A wide range of substances are grouped together into this class, which by its very nature challenges definitions and classifications. Inhalants include (1) solvents (liquids or semisolid substances that evaporate and include glue, shoe polish, toluene, and gasoline, among others); (2) aerosol sprays (volatile substances or gases such as spray paints, hair sprays, cleaners for computers, etc.); (3) gases (anesthetics for medical use such as ether, chloroform, butane, and refrigeration products); and (4) nitrites that include products containing butyl nitrite and amyl nitrite, known as "poppers," locker room deodorizers, or "rush," and nitrous oxide known as "whippets."

The physicochemical classification is: (a) gases or can easily become vapors at room temperature (without heating); (b) nonpolar molecules with high affinity for lipids and can therefore cross all biological membranes; (c) flammable; (d) usually lighter than water in their liquid form, but as vapors are heavier than air, meaning that they are not easily dispersed from rooms where they have been inhaled (Cruz 2011).

Since many substances meet these criteria, they can be classified on the basis of chemical structure (hydrocarbons, ethers, ketones, etc.), commercial use (solvents, anesthetics, propellants, etc.), physical state (gases, liquids, aerosols), or effects on the central nervous system (depressants, vasodilators, etc.). Each classification has its own limitations, and some substances may fit into several categories. For example, butane is a hydrocarbon gas used both as a fuel and a propellant; nitrous oxide is a propellant and also an anesthetic gas used in dentistry. Moreover, a single substance can have different names such as toluene, methylbenzene, phenylmethane, or toluol. This compounds the difficulties associated with inhalant research. Table 36.1 shows some commonly misused compounds and their synonyms and chemical structure, examples of commercial products, threshold limit values (TLV: maximum average concentration to which workers can be exposed 8 h/day, 5 days/week, without experiencing significant adverse health effects), and vapor concentrations in air that are dangerous to life and health (IDHL). This table also includes CAS#, a unique chemical abstract service number that may be used to obtain key information on individual compounds. A detailed table of the physicochemical properties of main inhalants can be found elsewhere (Bowen and Cruz 2014).

Although there is insufficient evidence to establish a scientifically based pharmacological classification of inhalants, it is possible to distinguish at least three different categories with various mechanisms of actions: (a) solvents, fuels, and

Table 36.1 Synonyms, products and safety limits of inhalants

Class	Compound	Structure	Synonyms	CAS#	Products	TLV (ppm)	IDLH (ppm)
Hydrocarbon, acyclic	*n*-Hexane		Hexyl hydride, dipropyl	110-54-3	**Gasoline**, solvents, glues, varnishes	50	1,100
Hydrocarbon, alicyclic	Cyclohexane		Hexamethylene, Hexanaphtene	110-82-7	Lacquers, resins, varnish removers, solvents, cigarette smoke	300	1,300
Hydrocarbons, aromatic	Benzene		Benzol, phenyl hydride, cyclohexatriene	71-43-2	Gasoline	0.5	500
	Toluene		Toluol, methyl-benzene, phenylmethane	108-88-3	Solvents, paints, thinners, glues, lacquers, gasoline, inks, cigarette smoke	50	500
	Xylene		Xylol, dimethyl-benzene, methyl toluene	1330-20-7	Cleaning agents, thinner. Used in printing, rubber and leather industries	100	900
	Ethyl-benzene		Phenyl ethane, ethyl benzol	100-41-4	Gasoline, paints, inks. Used as styrene precursor	100	800
	Propyl-benzene		Phenyl propane, isocumeme	103-65-1	Gasoline. Used in textile dyeing and printing	N.E.	N.E.
Hydrocarbons, halogenated	1,1,1-TCE		Trichloroethane, TCE, perchloroethylene, tetrachloroethane, methyl chloroform	71-55-6	Cleaning products, paints, correction fluids, degreasers	350	700
	1,1,2-Trichloro-ethylene		TCE	79-01-6	Solvents, dry cleaning products,, degreasers (car parts) Plastic spray fixative	50	1,000

	Diethyl-ether		Ethyl ether, octapentane, ethoxy ethane	60-29-7	Anesthetic, solvents, fuels	400	1,900
	Chloroform		Trichloromethane Methyl trichloride	67-66-3	Anesthetic, spot removers, precursor for refrigerants	10	500
	Halothane		Fluothane	151-67-7	Anesthetic	50	N.E.
Inorganic	Nitrous oxide		Dinitrogen monoxide	10024-97-2	Anesthetic, laughing gas, propellant (hair sprays, whipped cream, cooking spray), engine combustion enhancer	50	N.E.
Hydrocarbons, acyclic	Propane		Dimethyl methane, LP gas	74-98-6	Industrial fuel, refrigerant, aerosol propellant	1,000	2,100
	Butane		Methylethyl ethane, Freon 600 LP gas	106-97-8	Lighter fuel, gas tanks for cooking, refrigerant, aerosol propellant (deodorant sprays)	800	N.E.
Hydrocarbons, Halogenated	1,1-difluoroethane		Ethylene fluoride, Freon 152 a, R152a, HCF152a, Dymel	75-37-6	Propellant (PC duster), refrigerant (air conditioning)	1,000	N.E.
	1,1,1,2-Tetrafluoroethane		Freon 134 R134	811-97-2	Propellant (PC duster), refrigerant (car air conditioning systems)	N.E.	N.E.

Sources: PubChem, NIOSH ICSC (International Chemical Safety Cards), ATSDR (Agency for Toxic Substances and Disease Registry), Household Products Database, and Haz Map.
CAS# chemical abstract service number, *TLV* threshold limit value, *IDLH* immediately dangerous to life and health

anesthetics; (b) nitrous oxide; and (c) volatile alkyl nitrites. The first is the most extensive group and includes inhalants misused throughout the world in the form of gasoline, industrial solvents, adhesives, paints, sprays, inks, pen markers, and many other commercial products. Among solvents, toluene is the most frequently misused and the best-studied inhalant compound. It is the main component of paint thinners (mixed with xylene, ethylbenzene, and other solvents in different proportions), inks, adhesives, and degreasing agents. Commercial xylene (a mixture of the three isomers: ortho-, metha-, and para-xylene) is used in the leather and rubber industries and histology laboratories. The solvent known as 1,1,1-TCE or trichloroethylene is also present in correction fluids, but no longer produced in most developed countries because it is harmful to the ozone layer. Gasoline is a mixture of several solvents, which may or may not contain lead. Several anesthetic gases such as halothane, ether, and chloroform are included in the same group with solvents because they share some of the effects and mechanisms of action of misused solvents.

Nitrous oxide is in a class of its own because of its unique pharmacological profile and affinity for specific receptors. It is used as a propellant in whipped cream products and as an anesthetic gas for dental procedures. As for nitrites, they are smooth muscle relaxant and vasodilator drugs rather than depressant substances and are inhaled from small bottles, some of which "pop" when opened (hence the name "poppers") (Cruz and Bowen 2008).

36.2.1 Epidemiology: How Widespread Is Its Use?

Worldwide inhalant misuse has mainly spread among young people. Although there are variations in the age of onset, the trend in most countries is toward an increasingly early start. Age at first use is generally 6–8 years, while peak age for abuse is 14–15 years (O'Malley 2012). The period of risk for drug use initiation among special populations such as youth from Indian communities has been reported as between the ages of 10 and 13 years, with the onset among some individuals being as young as 5–6 years of age (Hillabrant 2001).

In the Americas, there are countries like Canada and the United States that have seen a decrease in consumption. However, in Latin America and the Caribbean, it is a growing problem and has gone from being a drug consumed by street children to one that is consumed by children and young students and even university students (OEA 2011).

According to a study on young Americans (Johnston et al. 2014), inhalant consumption increased from the late 1970s to the mid-1990s, especially in 8th, 10th, and 12th grade. Trends have changed and in 2001, consumption began to decrease. The last measurement in 2013 shows that annual prevalence was 5.2 % in 8th grade, 3.5 % in 10th grade, and 2.5 % in 12th grade. Despite the variations, the trend is for consumption to decline, a trend that is believed to be associated with information campaigns.

In Canada, the Report on Alcohol and Drug Use by Students (Young 2011) indicated that among 7th and 12th grade students, inhalants are the fourth most ever

consumed drug (2.2 % and 3.8 %), respectively, preceded by alcohol, cannabis, and ecstasy, and prevalence in the last year reached 2.6 % and 4.4 %.

In Mexico, this practice has experienced periods of increase and decrease among students in various regions. For instance, in Mexico City, annual prevalence increased from 4.4 % in 2006 to 7.5 % in 2009, to decrease again in 2012 to 5.9% among high school students, with use remaining stable after 2009 (Villatoro et al. 2012). More recent surveys show that inhalation rates have remained unchanged. According to the National Household Survey 2011 conducted among the population ages 12–65, annual prevalence of use in the previous year was low, 0.1 % with no significant modifications from 2008 (SSA et al. 2012). This same trend is reported by the Epidemiological Surveillance System that gathers information on cases seeking treatment in nongovernmental organizations. Inhalants were the drug of "impact" defined as the one which, according to patients, constituted their main problem of abuse in 7.6 % of patients in 2009 and 7.2 % in 2011 (SSA 2013).

In most Latin American and Caribbean countries, apart from tobacco and alcohol, inhalants are the most commonly used substance after cannabis, especially among high school students, although there are countries where it is the first drug of choice (OEA 2011).

The lowest prevalence of ever use has been reported in Venezuela (0.7 %), Dominican Republic (1.1 %), Honduras (1.6 %), Guatemala (2.1 %), and Nicaragua (2 %) in surveys conducted among high school students between 2003 and 2009. The lowest prevalence in the past year in this same population was reported in the same countries, together with Uruguay (1.4 %). And the lowest use last month was also reported in the same countries: with less than 0.4 % reporting use.

The highest prevalences in the three measurements ever use, in the past year and last month, were found in Brazil (15.6 %, 14.3 %, 9.9 %), Barbados (19.6 %, 9.9 %, 6.4 %), Guyana (21.7 %, 10.5 %, 6.9 %), Trinidad and Tobago (26.3 %, 13.2 %, 7.4 %), and Jamaica (28.1 %, 13.9 %, 9.4 %) in surveys conducted between 2004 and 2007.

College students also report use of these substances. In countries in the Andean Region, a study showed that during the past year, the highest prevalence was reported in Bolivia (1.8 %) followed by Colombia and Peru (1.4 % and 1.7 %) and Ecuador with 0.77 %.

There are also differences by sex: in Argentina, Bolivia, Colombia, Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama, Suriname, and Uruguay, men have higher rates. In countries such as Antigua, Barbados, Granada, and Trinidad and Tobago, rates are higher among women, especially in Jamaica where the proportion is over twice that of men. In the United States, girls in 8th and 10th grade have slightly higher consumption (OEA 2011). In Mexico, household surveys show that more males than females use solvents (ENA 2011), but among high school students, gender differences have vanished (Villatoro et al. 2012). A similar situation is observed in Ontario, Canada, among high school students, with no difference in rates last year by sex, 5.3 % and 5.9 % among males and females, respectively (CAMH 2011). In Chile in secondary students (13–17 years), last year prevalence was 3.7 % and 3.1 % for males and

females, respectively, and in Ecuador 3.1 % males and 2.2 % females reported having used in the last 12 months (UNODC 2010).

In Europe, rates for students between the age of 15 and 16 varied between 17 % in the Isle of Man and 15 % in Ireland to 3 % in Bulgaria, Ukraine, and Lithuania (ESPAD 2007). In Africa, solvents and inhalants were the seventh drug of choice with a prevalence of 3.2 % in 2009.

In 2008, in Central Asia, UNODC (2008) reported that inhalant consumption among young people had increased and in some cases exceeded that of cannabis. For example, Tajikistan has a prevalence over the past 12 months of 8.4 % for boys and of 4.2 % for girls. In the past month, the figure was 2.1 % for boys and 3.6 % for girls. In Kazakhstan, the prevalence for boys was 2.4 % as opposed to 2 % for girls in the past year and 1.3 % and 1.1 % in the past month. Kyrgyzstan reported 2.4 % of boys and 1.7 % in girls in the past year, and for the last month, the figures are 1.6 % and 1.1 %. An earlier survey in this country (2006) reported inhalants as the first drug of use, with 5.4 % ever use. Lastly, in Uzbekistan, figures for the past year are 0.4 % for boys and 0.3 % for girls and 0.3 % versus 0.2 % in the past month.

A final word of caution, the rates reported in this section of the chapter are drawn mainly from surveys, that not always use the same definitions, and furthermore, these sources might underestimate prevalence of use rates among difficult-to-reach populations, not included in survey approaches, such as street children and prisoners, described in the following section. Rates of use among these groups are considerably higher.

36.2.2 Use Among Special Populations

Studies conducted in different parts of the world show that young people from low-income, chaotic, broken, or abusive homes appear to have the highest rates of use (Oetting et al. 1988). According to O'Malley (2012), in the United States and Canada, long-term use of inhalants is more common in inner-city and remote rural community residency; it is also associated with lower socioeconomic class, Latin American immigration, and family dysfunction.

Villatoro et al. (2012), analyzed data from national household surveys in Mexico and, found that those drug users that reported having ever inhaled, as compared to cannabis users that had not experimented with these substances, came from more disorganized and violent communities and also reported having being involved in fights, selling drugs, and other problem behaviors more frequently. Storr et al. (2004) using data from a nationally representative population sample ages 12 and older in the United States ($n = 25{,}500$) examined whether living in disadvantaged communities increased the likelihood of coming into contact with drug dealers as compared with persons living in more advantaged areas, and found that the physical and social characteristics of a neighborhood determined the likelihood of becoming involved with drugs.

High inhalant abuse rates have also been documented among street children living in South America, Eastern Europe, and Asia (Forster et al. 1996;

Pagare et al. 2004). For instance, in a study conducted in Mexico in 100 cities, rates of use varied from 3 % among adolescents working on the streets to 72 % among those living in the streets; the substance of choice being toluene (Medina-Mora et al. 1999).

This practice has also been reported across indigenous communities in Australia and North America (Beauvais and Oetting 1988; Chalmers 1991). In these communities, lifetime prevalence rates of petrol sniffing among adolescents reach 50–60 % and appear to be associated with the isolation (both geographical and social), poverty, and unemployment prominent among these marginalized groups (Cairney et al. 2002). According to Remington and Hoffman (1984), inhalation of gasoline tends to occur in poor, isolated communities and on Indian reservations where unemployment is widespread and few organized social activities are available to youth.

The National Inhalant Prevention Coalition (NIPC) reported that 20 % of the Kickapoo Tribe is "addicted to spray paint," this group's drug of choice. According to this Coalition, it alleviates hunger, and the periods of intoxication last longer than those produced by alcohol. Users also report that paint-induced hallucinations are easily incorporated into tribal traditions (News Briefs, NIPC 1997). A survey of Navajo 8th graders found that almost 25 % have tried inhalants, with 12 % having used inhalants in the previous month. This survey reinforces the findings of other studies that report that the majority of inhalant abusers are young. Leal et al. (1977) also found that toluene abusers in Mexico City declared that solvent sniffing alleviated hunger and that they enjoyed the altered perceptions it produced.

36.2.3 Patterns of Use

As is the case with other drugs, inhalers can be classified as experimenters, regular users, heavy users, and persons with dependence. Among students, especially those in early adolescence, the most common pattern involves experimentation with a low proportion of regular users and an even smaller proportion of students that have developed dependence. For instance, among American and Australian students, experimental inhalant use rates during early adolescence are high (26 % of 12-year-old students), whereas the proportion that reports inhaling on a regular basis is over six times smaller (4 %) (Johnston et al. 2003; White and Hayman 2004). In Mexico City and Jalisco, experimentation rates (using one to five times) among young students (7–9 years of school) are also considerably higher (66 % and 76 %, respectively) than rates for use on over five occasions (44 % and 24 %) of all persons that have ever used (Villatoro et al. 2012; Chávez et al. 2013). This pattern differs from the one observed among adolescents living on the streets who are heavily involved in inhalation, with daily heavy use being the most common pattern combined with periods of complete abstinence (Medina-Mora and Berenzon 1997).

Few studies report dependence rates among them. Perron and colleagues (2011), using data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) household sample of persons ages 18 and older in the

United States, documented that 19.5 % of lifetime inhalant users met the criteria for DSM-IV inhalant use disorder (abuse 17.2 % or dependence 2.3 %).

Inhalants are usually "sniffed" directly from the container to the nose, but inhaling fumes through the mouth ("huffing") is also common. The open tube of glue or nail polish is usually placed close to the nose and the fumes are inhaled. Sometimes users heat substances to speed up the vaporization process which increases the risk of gas explosions. Other forms of use include inhaling from damp rags or shirt sleeves or from plastic or paper bags ("bagging"). Fatal accidents may occur when the inhaler places the whole bag over his head; balloons filled with substances such as nitrous oxide have also been reported (NIPC 1997). Some authors have reported that the route of administration is related to environmental factors such as the presence of police and the need to disguise use (Medina-Mora and Berenzon 1995). A case study in India reports petrol inhalation by a 10-year-old boy who began to inhale it accidentally by putting his face to the keyhole of the petrol tank on his father's motorbike (Basu et al. 2004).

Preference for specific substances varies according to the characteristics of the groups that use them and their effects; Takagi et al. (2010), for example, when assessing preferences for types of paint among inhalers in Australia, found that compared to non-chrome users, chrome-using groups was more likely to report deliberately inhaling to experience altered perceptions (such as visual and auditory hallucinations). A greater proportion of chrome users reported that the perceptual alterations they experienced after sniffing paint differed between paint colors, with more vivid hallucinations being produced by chrome colors. Similarly, Leal et al. (1977) reported that children living on the streets in downtown Mexico City preferred pure toluene for its psychotropic effects and lower level of toxicity. Cruz and Domínguez (2011) have also documented hallucinations among heavy inhalers in Mexico who use toluene or a mixture of solvents.

Common choices for solvents among American Indian youth and Alaskan Natives are gasoline (28 %), glue (23 %), paint removers and nail polish remover (18 %), and paint sprays (17 %). In this group, as is often the case with street children (Medina-Mora et al. 1997), most of the substances inhaled contain mixtures of chemicals, making it almost impossible to determine which compounds are responsible for the effects experienced by the abuser and observed by therapists (Oetting et al. 1988).

Trotter et al. (1977) reported that inhalant abuse was sometimes combined with drinking the liquid residue left in aerosol cans after sniffing the propellant (Trotter 1997). Hillabrant (2001) published interviews with Navajo adolescents who reported the fad of drinking hair spray, users of which faint after five bottles an hour.

Some groups in Mexico use "compressed air" at special gatherings known as "perreos" or "grinding, booty dancing, bumping, or housing" in the Caribbean. Inhalants and alcohol are the substances consumed; attendees may buy a piece of rag soaked in toluene that has been flavored. Risky sexual behavior and fights are common (Gutiérrez et al. 2007). Having sex under the effects of poppers has been documented among gays and; use of these substances has been associated with

having casual partners (Lampinen et al. 2007). In Brazil, lança perfume (chloroform/ether) is used by students (Mesquita et al. 1998) mainly by those pretainig to a upper-class ones (Sanchez 2012).

36.3 Health Effects

Inhalants: Short-term effects are similar to alcohol and other central nervous system inhibitors as regards initial stimulation and persistence. They act as anxiolytics, antidepressants, and anticonvulsants and are associated with impaired motor coordination, emotional lability, and difficulty speaking. Chronic effects include neurotoxicity, cognitive impairment, headaches, diminished sensorial abilities (loss of vision, audition, and coordination), and an increase in mental disorders and sleep disturbances.

There is evidence that the more widely used inhalants share cellular mechanisms and have similar effects to other drugs, particularly depressors of the central nervous system (Cruz 2011) although the use of these substances has also been associated with illusions and hallucinations (Cruz and Dominguez 2011). When used by pregnant rats, they affect development, and irregular heartbeat during intoxication has also been described (Cruz et al. 2003). Unfortunately, a significant shortage of information remains, despite the increase in research projects addressing the neurobiology of inhalants; the majority are still conducted on toluene. Little is known of abstinence, and researchers do not know the extent to which cognitive or other effects may be reversible, although some laboratory experiments with enriched environments have provided evidence of reversibility (Lubman et al. 2008; Páez-Martínez et al. 2013).

36.3.1 Acute Effects

Inhalants vary in their chemical composition and consequently in how and where they act. In fact, it is rather surprising that such a dissimilar group of substances should have the same effects, although this is partly due to their common administration route. Misusing inhalants implies introducing gases other than air into the body causing poor brain oxygenation (hypoxia) and the attendant deleterious consequences. This happens with all inhalants regardless of their pharmacological profile and constitutes a significant health hazard in itself.

Once in the body, inhaled vapors rapidly achieve various specific molecular targets to induce a state of intoxication similar to that produced by other central nervous system depressant drugs such as alcohol and barbiturates. The pulmonary route is highly efficient because the lungs are profusely irrigated and have extensive absorption surface. This results in rapid intoxication, which is, however, short-lived due to inhalants' high volatility. In order to maintain the effects, users repeat the experience every few minutes to maintain the desired level of active substance in the brain.

Several solvents and fuels produce a transient state of excitation followed by a more persistent sedation, lack of motor coordination (ataxia), slurred speech, cognitive impairment, and slow reactivity toward the stimuli (Sharp et al. 2008). At high concentrations, illusions and hallucinations are common and known to play an important role in the motivation to inhale and socialize (Cruz et al. 2011; MacLean 2007). When anesthetic gases are intentionally used, sedative effects combined with psychoactive actions can be extreme.

Other effects depend on the type of compound inhaled. Let us consider the case of solvents. The respiratory system is the first to come into contact with the irritant vapors of these substances, producing coughing, frequent nose bleeding, rashes, and dry skin around the nose and mouth. Irritation is frequent in all parts of the body (usually hands and arms) that come into contact with rags or tissue papers soaked with solvents because – as degreasing agents – solvents damage the dermal lipid layer. Among this type of inhalants, apparently only toluene produces notoriously detrimental effects in acoustic perception, initially described as a strong buzz and chronically associated with inner ear damage. On the other hand, if the gas inhaled is nitrous oxide (also known as laughing gas), hilarity, mood swings, altered perception, and anesthesia may occur. Inhalation of 1,1-difluoroethane, a gas used as a propellant in computer dusters, can cause frostbite in the tongue, mouth, larynx, and other soft tissues in addition to its psychoactive actions.

Volatile alkyl nitrites differ from all other inhalants because they produce vasodilation and smooth muscle relaxation rather than cognitive effects. Amyl nitrite was introduced as medication for the treatment of angina pectoris until it was replaced by nitroglycerine. Amyl, butyl, and isobutyl nitrites are sought as sexual enhancers due to their ability to increase genital irrigation. These compounds decrease blood pressure, increase heart rate, and, under some circumstances, can cause syncope. These harmful cardiovascular effects may be enhanced if alkyl nitrites are combined with phosphodiesterase-5 inhibitors, the active ingredients of medications used to treat erectile dysfunction.

36.3.2 Chronic Effects

Repeated inhalant use produces chronic irritation of the respiratory airways with breathing difficulties and increased frequency of respiratory illnesses, anosmia (decreased capacity to detect odors), and general cognitive impairment. Chronic inhalant users have a higher incidence of neurobiological abnormalities including diffuse cerebral and cerebellar atrophy, enlarged brain ventricles, and general white matter damage. These abnormalities have been correlated with attention dysfunction, impaired motor control, and memory loss together with reduced speed of information processing, among other detrimental effects (Yucel et al. 2008). Inhalation of toluene-based products can cause hearing loss, visual impairment, and severe ataxia (Filley et al. 2004).

Benzene, a component of gasoline, produces anemia and leukemia because it impairs blood cell formation in the bone marrow. The toxicity associated with

gasoline inhalation may not only be linked to benzene but also to the presence of lead in countries that do not use unleaded gasoline. Hexane, another organic solvent used in inks and other products, causes peripheral neuropathy because it is metabolized to 2,5-hexanedione, a highly toxic compound.

Halogenated compounds, in other words, those containing chloride, fluoride, or bromide in their structure, such as 1,1,1-trichloroethane, trichloroethylene (a degreasing agent and spot remover), halothane (a liquid anesthetic), or 1,1-difluoroethane (PC duster) can produce liver and kidney failure as well as cardiac arrest.

Repeated exposure to nitrous oxide produces a vitamin B_{12} deficiency, which may lead to damage to the neuron's myelin sheath manifested as ascending lower extremity weakness and numbness (Lin et al. 2011). As for nitrites, chronic users of this compound can experience bilateral vision loss due to retinal damage (Audo et al. 2011).

36.3.3 Prenatal Effects

The fact that the gender gap is being reduced poses specific challenges for service providers and researchers owing to the harmful effects of inhalants in women of reproductive age. A fetal solvent syndrome, similar to that caused by alcohol, has been described in babies born from mothers who used inhalants during pregnancy. This syndrome includes facial anomalies, delayed growth, and impaired neurobehavioral development (Bowen 2011). Low weight at birth and craniofacial abnormalities have also been documented in both clinical and preclinical studies (Hannigan and Bowen 2010). Follow-up studies of children exposed to inhalants during gestation have shown growth retardation, learning impairment, cerebellar dysfunction (affecting balance), language deficiencies, and hyperactivity. It is worth mentioning that some of these studies cannot rule out the use of other drugs and, in fact, it is fairly common for inhalants to be used in combination with other psychoactive substances. However, animal studies in which environmental conditions are controlled and only solvents are used support these findings.

36.3.4 Molecular Effects

The available evidence indicates that toluene, the best-studied misused solvent, has a complex mechanism of action, which includes effects on diverse molecular targets. Although detailed description of toluene's mechanism of action is beyond the scope of this chapter and has been reviewed elsewhere (Bowen et al. 2006), a few relevant data might be worth noting. Toluene inhibits the function of certain channels activated by excitatory neurotransmitters such as the glutamatergic NMDA receptors (Cruz et al. 1998) and nicotinic receptors (Bale et al. 2005a). At similar concentrations, toluene enhances the function of inhibitory neurotransmitter receptors such as GABA (Bale et al. 2005b) and glycine (Beckstead et al. 2000). Calcium channels, potassium channels, and sodium channels are also

affected by toluene (Shafer et al. 2005; Cruz et al. 2003; Del Re et al. 2006). Like other drugs of abuse, toluene increases dopamine release in key areas of the dopaminergic mesolimbic system. Less data are available on other solvents, but evidence indicates that at least the effects on GABAergic and glutamatergic systems are common to many substances including the majority of inhaled gases.

36.3.5 Morbidity and Mortality

Mortality is associated with this practice. Sudden sniffing death is a rare but serious complication that may occur at any time, even after single use; in other words, it is not necessarily associated with repeated or prolonged exposure. Death can be due to a combination of factors including poor oxygen supply, a direct cardiac effect (arrhythmias), and sensitization to catecholamine stimulatory effects. Sudden death may occur when an intoxicated user is startled because catecholamines are released, the heart function is increased, and cardiac arrest becomes more likely (Bowen 2011). It has also been reported as a result of adrenaline surge. It can occur during abuse or in the next few hours because solvents, dissolved in lipid-rich cell membranes, dissipate slowly.

Other causes are derived from the interaction between the substances abused, the user, the route of administration, and the environment. Suffocation and trauma may occur when a user puts a plastic bag sprayed with a solvent over his or her head to enhance the amount inhaled; the plastic bag may occlude the airway if the user loses consciousness. Death by aspiration, usually of vomit, is similar to that observed for alcohol and other depressants and results from a combination of a decreased level of consciousness and the loss of protective airway reflexes. Risk of accidents is high as users become less inhibited and less alert and oriented, which facilitates engagement in risky behaviors (Williams et al. 2007).

Lifestyles of certain subgroups such as street children raise the burden related to violence and increase the risk of HIV from sexual abuse and prostitution (Medina-Mora et al. 1997). In a survey conducted in 100 cities in Mexico among working children and adolescents ages 6–17, Medina-Mora found that fewer than 1 % declared prostitution as their source of income. Increased risk of seroconversion among the street population has been reported in other sites (Roy et al. 2003).

The Toxic Exposure Surveillance System (TESS) database of the American Association of Poison Control Systems showed 63 deaths in 11,670 cases of intentional inhalant abuse reported from 1996 to 2001 to poison control centers in that country, linked to gasoline inhalation (45 %), air fresheners (26 %), and propane/butane (11 %) (Spiller 2004). In two particular states, Virginia and Texas, a higher rate was found, 39 and 144, respectively, the majority linked to fuel inhalation.

There is a wide range of diseases linked to this practice that includes ichthyosis-like dermatitis on the extremities, decreased visual acuity, toxic hepatitis, distal renal tubular acidosis, metabolic acidosis, leukemia, and aplastic anemia.

There is also evidence of tolerance, dependence, and withdrawal, among many other disorders: despite this evidence, there is insufficient data to allow the assessment of the proportion of the global burden of disease related to this behavior (Degenhardt and Hall 2012).

36.4 Correlates

In a review published in 2008, Medina-Mora and Real found evidence of high rates of psychiatric comorbidity, mood, anxiety, and personality disorders being common among lifetime inhalant users. They also reported a higher prevalence of lifetime dysthymia and anxiety disorders among female inhalant users, although a lower prevalence of antisocial personality disorder. Among inhalant users with comorbid disorders, those who developed social or specific phobia had experienced the onset of these disorders prior to the initiation of inhalant use; all other mood and anxiety disorders usually developed following the onset of inhalant use. Odds of psychiatric disorders were higher for inhalant users who were women, poor, and less educated and with an early onset of inhalant use, family histories of psychopathology, and personal histories of substance abuse treatment.

These same authors also concluded from their review of the literature that among incarcerated youth, compared to users of other substances, inhalant users showed significantly higher levels of criminal behavior, antisocial attitudes, current psychiatric symptoms, earlier onset of offending and substance use, and more extensive histories of head injury, kidney disease, hormonal problems, mental illness, suicidality, trauma, and substance-related problems (Medina-Mora and Real 2008).

The complexity nature of this problem as described requires complex, culturally sensitive interventions at the individual, familial, and community level and public policies designed to reduce the risk associated with the substances themselves and to control availability with a particular focus on children and adolescents, the modification of the social determinants underlying this disorder, the reduction of health disparities, and the promotion of development.

36.5 Prevention

Prevention entails various strategies, including education, skill building, environmental changes, and policy development. School setting prevention programs suggest the importance of involving the whole community: students, teachers, administrators, school nurses, guidance counselors, school social workers, school psychologists, librarians, parent volunteers, school police and safety officers, coaches, clerical staff, cafeteria workers, custodians, and bus drivers (Virginia Department of Education 2007).

Other authors report that efforts to prevent volatile substance abuse should focus on community interventions. In particular, information should be distributed to health workers, educators, media representatives, and parents (Dell 2003).

Many strategies focus on educating very young children about the dangers of inhalants and disseminating messages that depict inhalants as poison. In Texas in the United States, some of these programs have attempted to redefine the problem as a public health rather than a substance abuse issue. This perspective facilitates the involvement of community partners, nurses, emergency room personnel, medical associations, and poison treatment centers.

Other prevention interventions have been developed and provide educational materials and resources for families, school, and media. Products include staff training and curricula for schools and resources for teaching parenting skill (NIDA 2005).

Some populations require special attention among them the Indigenous populations. Interesting cultural adaptations can be found, for example, in programs for Alaskan Natives aimed at making students aware of the dangers of inhalants (Hillabrant et al. 2001). A program for young migrants from Morocco, included attention for basic needs and identification and intervention with those recently involved with inhalants. The program also included workshops on health promotion, sports and art activities (Foundation Search 2002). As in treatment, prevention includes teaching and helping children, teenagers and their families to build strengths, increase cultural self-identity, develop social and emotional skills (Dell et al. 2003).

36.6 Treatment

Considering the broad range of compounds included in the inhalants category, several approaches are required to deliver effective treatment to chronic users.

36.6.1 Recovery Potential and Treatment

Despite the impact of the negative effects of inhalant misuse reviewed in this chapter, there is some evidence of the potential for recovery from deleterious cognitive and neurological effects that occurs following abstinence from solvent misuse, depending on the extension and duration of inhalant misuse (Dingwall and Cairney 2011). Bowen and Cruz (2014) described evidence indicating that the myeloneuropathy associated with chronic use of nitrous oxide improves with inhalant discontinuation and vitamin B_{12} supplementation (Alt et al. 2011) and that retinal damage produced by chronic nitrite inhalation can recover after cessation (Audo et al. 2011). Unfortunately, some negative sequelae, such as benzene-induced leukemia or liver toxicity produced by halogenated compounds, would appear to be more devastating. Support in the form of cognitive behavioral therapy, attention to organic damage (e.g., hearing or sight loss), and treatment of psychiatric comorbid disorders when needed are important components of successful treatment programs.

In this same review, Bowen and Cruz (2012) conclude that to date, there is no available pharmacological therapy for treating this substance use disorder, but some

evidence of limited success has been found, such as using risperidone to control paranoid psychosis in a man who had been inhaling gasoline and carburetor cleaner daily for 5 years (Misra et al. 1999). Other authors have reported that the severity of the symptoms of inhalant-induced psychotic disorder, which was reduced when treated with either carbamazepine or haloperidol (Hernandez-Avila et al. 1998). Moreover, daily administration of lamotrigine decreased craving in a 21-year-old man with a 4-year history of inhalant misuse (Shen 2007). More investment in research will lead to better pharmacological treatment.

Psychosocial interventions have proved effective. These include housing, programs aimed at promoting school attendance and retention, alternatives such as art activities, counseling, and outreach for children at risk of becoming street children (Echeverría and Tavera 2007).

Good treatment models are an important factor in improving the quality of life of those affected and reducing the costs for society; availability of services and service utilization complete the equation. We know from the World Mental Health Survey that the treatment gap for mental disorders including substance use disorders is important, between 35.5 % and 50.3 % in developed countries and 76.3 % and 85.4 % in developing countries (Demyttenaere et al. 2004), and that the treatment gap in some countries such as Mexico is similar for substance use disorders (Borges et al. 2007) but few studies report rates of service utilization by type of substance in subjects, with dependence on inhalants.

Perron and colleagues (2011) within the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) reported that among those with dependence (2.3 %), 66 % were using some sort of service, mainly 12-step programs (68.5 %) followed by drug rehabilitation programs (61.2 %) and private practitioners (55.6 %). A total of 15 % reported at least one barrier to receiving services with the low-income group reporting more barriers (22.8 %). The most common treatment barriers were related to a lack of understanding of what dependence means; between 41 % and 43 % declared that "the individual should be strong enough to handle it alone" or "thought the problem would get better by itself." The same proportion (42 %) reported that they did not want to seek help. In around a third (28.8 %), barriers were related to stigma, "feeling too embarrassed to discuss it with anyone." Lack of resources was reported by one fifth of those with dependence (23.2 %). This suggests the need to introduce policies to increase both treatment and service utilization coverage.

36.6.2 Policy Options

As reviewed in this chapter, inhalant misuse is a phenomenon characterized by significant inequalities as regards the social context of the most severely affected users who tend to come from poorer, more disorganized, or isolated communities, who are more likely to be exposed to low-quality substances, violence, and other adverse experiences. They also have fewer education and job opportunities and worse health outcomes and socioeconomic consequences such as dropping out of school,

unemployment, employment in the informal sector, stigmatization, and barriers to accessing health care. This scenario calls for the inclusion of intervention efforts to reduce these social determinants within a framework of community intervention.

Some recommended measures include meeting the need for education and employment, ensuring health care, and providing alternatives to inhalation such as sports and other recreational and artistic activities along with actively seeking persons at risk of using substances and counseling (Rodgers 1999). Community interventions aimed at reducing disorganization and violence include environmental design, urbanization, the participation of organizations that provide support to families, prevention programs that promote group cohesion and conflict resolution without violence, and in general empowering communities to make accurate diagnoses, develop action plans, formalize processes, and monitor progress (World Bank 2011; Zakocs and Edwards 2006).

A good example of a policy aimed at reducing the risk associated with the toxicity of substance*s* was the development in Australia of Opal fuel, which contains very low levels of the aromatic compound that causes intoxication, benzene, toluene, and xylene, making it less attractive for inhalation (d'Abbs and MacLean 2008). Other examples of this type of interventions are the modifications of the formula for aerosol spray paints replacing aromatic chemicals toluene and xylene with less intoxicating ones (ADCA 2010) and the development of water-based glues for school use.

Controlling availability with a special focus on children and adolescents in supermarkets, hardware stores, or service stations and setting up commercial organizations to prevent the sale of inhalants to these population groups are other examples.

Harm reduction interventions aimed at educating about the particular dangers associated with certain substances and means of administration, to reduce the risk of accidents and mortality, are controversial but may be considered as a first step when approaching heavy user populations.

Legislation can provide governments, retailers, and community and health workers with the means to address misuse such as removing products from users or stores, moving users to safe places, mandating treatment, and placing restrictions on the packaging and sale of inhalants. Existing laws do not usually make inhalant possession illegal (ADCA 2010).

Educating frontline health workers, teachers, police, and community counselors requires training them to identify those at risk, evidence-based interventions, and referral to services.

Parents, teachers, police, and community organizations must be informed about substances with the potential for abuse and the identification of persons that are abusing, proper handling, and referral of cases are all necessary to reduce inhalant misuse related harms.

Investment in basic and applied research on substance misuse is required, to ensure that research translates from the molecular to the clinical level and to the community.

36.7 Conclusion

Inhalants are the only drugs of abuse defined by the route of administration rather than their attributes, specifically similar mechanism of actions or common pharmacological effects. They are substances of abuse not included in the International Regulations and are seldom a priority for health and social interventions or for research funding. Inhalant products have legal uses in industry and households and are therefore inexpensive and readily available. They are more commonly used by young students and children and adolescents from poor sectors of society or heavy drug users when they lack access to other substances.

The short-term effects of inhalants are similar to those of alcohol and other central nervous system depressants and may produce impaired motor coordination, emotional lability, and difficulty speaking. Chronic effects include neurotoxicity, cognitive impairment, headaches, diminished sensorial abilities (loss of vision, audition, and coordination), and an increase in mental disorders and sleep disturbances. Inhalant use prevention involves different strategies, including education, skill building, environmental changes, and policy development. There is little research focusing specifically on the different compounds that are included in this heterogeneous group of substances classified as inhalants. Evidence-based treatment for inhalant abuse and dependence is scarce. However, treatment should include supportive psychotherapy, family and psychosocial interventions general healh care, proper nutrition, and vitamins or nutritional supplements. The long-term outcome of this addiction is usually progressive neurocognitive deterioration with multiple medical complications.

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Treatment of Anabolic-Androgenic Steroid Related Disorders

37

Harrison G. Pope Jr. and Gen Kanayama

Contents

Abstract

The family of anabolic-androgenic steroids (AAS) comprises the male hormone testosterone and its many synthetic relatives. Although elite athletes have used AAS for muscle and performance gains since the 1950s, widespread AAS use did not emerge into the general population until the 1980s. Thus, AAS abuse is the youngest of the world's major forms of substance abuse, with most AAS users still below age 50. There are now some tens of millions of AAS users worldwide, primarily male and primarily in Western societies. Contrary to

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common belief, most AAS users do not engage in competitive athletics, but simply want to become leaner and more muscular. AAS users may occasionally experience serious psychiatric effects, including hypomania or mania during AAS exposure and depression during AAS withdrawal. Long-term medical effects include especially cardiomyopathy, atherosclerotic disease, and prolonged suppression of the hypothalamic-pituitary-gonadal axis. About 30 % of AAS users develop dependence syndromes, likely caused by a confluence of psychosocial factors (e.g., using AAS to "self-treat" muscle dysmorphia), neuroendocrine factors (e.g., repeatedly resuming AAS use to self-treat hypogonadism during AAS withdrawal), and hedonic effects. A hedonic component is supported by evidence that male hamsters will self-administer testosterone to the point of death. Treatment of AAS dependence remains largely empirical, in part because most AAS abusers are still too young to have developed adverse effects. Thus, few have desired or sought treatment. This situation may change in future decades, however, as growing numbers of aging AAS users enter the age of risk for long-term adverse effects.

37.1 Introduction

Anabolic-androgenic steroids (AAS) are a family of hormones that includes the natural male hormone testosterone and more than 100 other synthetic relatives of testosterone (Kanayama et al. 2010b; Kanayama and Pope 2012). All AAS possess both anabolic (muscle building) and androgenic (masculinizing) properties; it is equally correct to refer to these hormones simply as "androgens" (Kanayama and Pope 2012). Since the 1950s, AAS use has been widespread in elite athletes and bodybuilders, who have long recognized that AAS allow them to achieve muscle gains far beyond those attainable by natural means. However, it was not until the 1980s that AAS use began to emerge from the elite athletic world and into the general population. Now, some two million American men, and millions more worldwide, have used these drugs illicitly. Most of these newer users are not competitive athletes at all, but simply men who wish to get leaner and more muscular (Kanayama and Pope 2012; Melnik 2009). The majority of these men are in their 20s or 30s, contrary to widespread belief, with only a minority starting AAS use as teenagers (Kanayama et al. 2007). AAS use is very rare in girls and women, since women do not often aspire to be extremely muscular and are also vulnerable to the androgenic effects of AAS such as beard growth, deepening of the voice, and masculinization of secondary sexual characteristics. Although some anonymous surveys have suggested that substantial numbers of teenage girls have used AAS, these surveys have almost certainly produced inflated estimates as a result of false-positive responses on questionnaires (Kanayama et al. 2007). For these reasons, the following discussion will be focused primarily on treatment of male AAS users, although the general principles expressed would presumably apply to the rare cases of women as well.

Although AAS pose important medical and psychiatric risks (see below), AAS users rarely seek treatment. Indeed, one recent study reported that 56 % of illicit AAS users had never disclosed their AAS use to any physician that they had seen (Pope et al. 2004). There are several reasons for this phenomenon. First, many AAS users perceive their use of AAS to be a positive and healthy activity, when combined with intensive exercise and optimal diet as part of the "bodybuilding lifestyle." Commercial and societal forces are partly responsible for this misperception of AAS: muscular male bodies are portrayed as an ideal in advertising, magazines, television, and movies. Even children's action toys, such as "G.I. Joe," have grown from ordinary-looking men in the 1960s and 1970s to muscle-bound specimens by the 1990s. Advertisers sometimes tout their products as "on steroids," but they would never claim that their products were "on marijuana" or "on cocaine." Given this societal climate, it is not surprising that AAS users rarely perceive their drug use as a psychiatric disorder requiring treatment (Kanayama et al. 2010b).

Second, AAS differ from conventional drugs of abuse. Most drugs of abuse described in this volume deliver a prompt "reward" of intoxication immediately after ingestion. However, AAS produce little or no reward of intoxication; instead, the user is seeking a long-term reward in the form of a more muscular body, athletic success, or admiration from peers or potential sexual partners. Thus, conventional methods of treating substance abuse may be inappropriate unless modified specifically for AAS users (Brower 2009).

Third, AAS users often have little respect for doctors. Internet sites for illicit AAS users are replete with derogatory remarks about health professionals. AAS users often regard physicians as "geeks" or "pencil necks" who have no understanding of the bodybuilding world. In one recent study, for example, 40 % of AAS users reported that they trusted information about AAS from their drug dealers at least as much as information from any physician that they had seen (Pope et al. 2004). There is some basis for this distrust: for decades, many medical professionals asserted that AAS were ineffective for gaining muscle mass. This claim, based on two decades of seriously flawed studies, caused doctors to lose their credibility among many athletes (Kanayama et al. 2008). Now, most professionals finally concede that AAS are effective for gaining muscle mass, but still remain largely uninformed about the extent and nature of the AAS-using subculture. Several recent papers have stressed that clinicians should attempt to become more familiar with AAS and AAS-associated syndromes (Kutscher et al. 2002; Melnik 2009).

Given the above considerations, it is understandable that AAS users rarely request treatment to stop using these drugs. Nevertheless, there are a number of specific situations that bring AAS users to the attention of clinicians. These include (1) AAS-dependence syndromes, (2) hypomanic and manic syndromes during AAS exposure, (3) syndromes of depression and anxiety associated with AAS withdrawal, (4) body-image disorders associated with AAS use, (5) co-occurring substance use disorders, (6) medical conditions associated with long-term AAS use, and (7) forensic situations, such as cases of AAS-induced violence or criminality. In the sections below, we begin with a general discussion of

the initial identification and assessment of AAS users and continue with each of the seven clinical issues enumerated above.

37.2 Identification and Assessment

37.2.1 Identification

AAS use is one of the few types of substance use where a diagnosis is often suggested simply by looking at the patient as he walks through the door. As we have described elsewhere (Kouri et al. 1995), there is a fairly sharp upper limit of muscularity that can be achieved by a lean individual without the help of drugs. We have published a formula to calculate muscularity, expressed as the "fat-free mass index" (FFMI), which clinicians can apply if they know the height, weight, and approximate percentage of body fat of the patient (Kouri et al. 1995). Men who have low body fat and display an FFMI of greater than approximately 26 kg/m^2 are almost certainly using drugs even if they deny it. Clinicians who suspect AAS use in any patient should follow several guidelines to take a specific history.

37.2.2 History

The clinician may lead into the topic of AAS by asking about athletic or fitness-related activities. Young men who lift weights regularly are at greatest risk to use AAS (Brower 2009). Other lead-in questions include the use of over-the-counter and mail-order dietary supplements such as vitamins, minerals, amino acids, and creatine. The use of such legal performance- or image-enhancing substances is commonly associated with use of illicit substances such as AAS (Hildebrandt et al. 2011). Finally, has the patient ever tried AAS or thought about using them? Patients thinking about AAS use are good candidates for prevention. Why is the patient interested in using, and what has prevented the patient from using to date? In addressing these questions, it is particularly critical for the clinician to be nonjudgmental while still discouraging use.

For patients who admit having tried AAS, both the perceived benefits and any adverse consequences of use are important to determine. The dates of first and last use, the names and doses of AAS used, sources of drugs, and routes of administration should be ascertained. Patients who inject AAS should be asked about needle sharing, although fortunately this practice now appears to be rare among AAS users (Ip et al. 2011). Sources of drugs include prescriptions, diversion from the legal market (including the veterinary market), and the illicit market. Unlike many other drugs of abuse such as heroin and cocaine, AAS are legally available without a prescription in many countries outside of the United States. Thus, potential AAS users can easily travel to nearby countries and also find Internet sites offering to sell AAS from overseas (Brennan et al. 2013). Drugs purchased through these sites, and then shipped by mail into the United States, often reach users without

being intercepted. Patients and clinicians should remember that drugs obtained from the illicit domestic market and from overseas sources are frequently counterfeit, adulterated, falsely labeled, and sometimes non-sterile. Thus, the user does not necessarily know what and how much he is taking.

Inquiry into the patterns of use is also important. Illicit AAS users typically combine ("stack") multiple types of AAS, including both oral and injected intramuscular forms, in order to achieve doses that are 10–100 times the amounts ordinarily prescribed for therapeutic indications (Ip et al. 2011; Kanayama et al. 2010b). Such doses may result in total AAS serum concentrations that may exceed 50 times natural male physiologic concentrations of testosterone (Kanayama and Pope 2012). AAS are usually taken in "cycles" (courses) of 4–16 weeks or more, often characterized by taking small doses at the beginning, building to large doses and combinations in the middle, and tapering doses at the end – a pattern referred to as a "pyramid." The clinician gains useful information when exploring the role of cycling with an individual AAS user. Does the patient cycle off AAS to avoid testing positive on drug screening? Does the patient cycle off AAS to give his body a rest, allowing his endogenous hormonal system a chance to regain normal functioning? Does the patient experience depression or other withdrawal symptoms during "off periods"? Dependent users may eliminate cycling altogether in favor of prolonged, continuous use in order to avoid withdrawal symptoms (see below).

Finally, a history of other drug abuse should be obtained. Users often combine other drugs with AAS to augment performance- and image-enhancing effects (e.g., human growth hormone, insulin-like growth factor I [IGF-I], human chorionic gonadotropin, clenbuterol, thyroid hormones, insulin, etc.), to reduce undesirable side effects such as gynecomastia (e.g., tamoxifen, letrozole, anastrozole), and to mask urine testing (e.g., probenecid, diuretics) (Hildebrandt et al. 2011; Ip et al. 2011). Also, in contradiction to the image of the healthy bodybuilding lifestyle, a large portion of AAS users display a history (and often an extensive history) of other forms of classical substance abuse or dependence (Dodge and Hoagland 2011; Garevik and Rane 2010; Kanayama and Pope 2012; Skarberg et al. 2009).

37.2.3 Physical Examination

The physical examination is essential to detect the somatic consequences of using AAS. Generalized muscle hypertrophy with a disproportionately large upper torso (neck, shoulders, arms, and chest) is readily apparent. The skin is examined for acne (on the face, shoulders, and back) and needle marks in large muscles (especially the gluteals, but sometimes the thigh and deltoids). Gynecomastia, caused by metabolic conversion of excess testosterone to estrogen, may be detectable by palpation or even simple observation in some men. By contrast, the testicles become atrophic as they shut down testosterone production when exogenous AAS are administered in high doses; this may lead to azoospermia and sterility (de Souza and Hallak 2011; Kanayama et al. 2010a). Male pattern

baldness, hirsutism, hypertension, hepatomegaly, right upper quadrant tenderness, jaundice, and prostatic hypertrophy are also possible, but are not reliably associated with AAS use. In women, hirsutism, deepening of the voice, and clitoral hypertrophy may be detected.

37.2.4 Mental Status Examination

The clinician should assess the patient's appearance for excessive muscularity as described above, sometimes disguised by oversized clothes, especially in patients with muscle dysmorphia who become preoccupied that they do not look big enough and hence wish to hide their bodies (Rohman 2009). The patient's cooperation may vary depending on his defensiveness or denial of AAS use. Speech and sensorium are generally normal. However, if the patient is experiencing hypomanic or manic symptoms from current AAS use, he may display irritability, agitation, and possibly grandiose beliefs. Patients experiencing depression from AAS withdrawal may exhibit depressed mood, dysphoria, anxiety, psychomotor retardation, and possible suicidal ideation.

37.2.5 Laboratory Examination

Laboratory abnormalities reported in AAS users are summarized in Table 37.1. Standard urine screens for drugs of abuse do not include AAS, so urine testing for AAS must be performed at a reference laboratory. Such testing can detect only recent AAS use: orally active AAS disappear from the urine within weeks, and most intramuscular preparations within a few months. However, given the association between AAS use and other illicit drug use, standard urine screens for illicit drugs should also be ordered.

Important blood chemistries include skeletal muscle enzymes, but these can be elevated even in non-AAS users after intensive weight training. AAS users may occasionally display pronounced elevations of creatine kinase from rhabdomyolysis. Standard "liver function tests," such as transaminases and lactic dehydrogenase, are nonspecific, since these enzymes are also present in the muscle and may be elevated from weight training (Dickerman et al. 1999). Many AAS users are erroneously thought to have liver disease when in fact their elevated transaminases are entirely muscular in origin. Elevation of chemistries specific to the liver, such as bilirubin and gamma-glutamyltransferase, may suggest true hepatic abnormalities.

HDL cholesterol is typically decreased during AAS use, particularly when individuals use orally active, 17α-alkylated AAS such as methandienone (Dianabol), oxymetholone (Anadrol), or stanozolol (Winstrol). The total cholesterol/HDL ratio, typically considered normal when less than 5.0, may be grossly elevated, with some men in our experience achieving ratios of greater than 20 as a result of extreme decreases in HDL levels. Such high ratios are likely associated with markedly increased atherogenic potential and may well contribute to the

Table 37.1 Laboratory abnormalities in anabolic-androgenic steroid users

Blood work	
Muscle enzymes	↑ ALT, AST, LDH & CK
Liver function tests	↑ ALT, AST, LDH, GGT & total bilirubin (caution: ↑ ALT, AST, & LDH are often muscular in origin and do not indicate liver disease)
Cholesterol levels	↓ HDL-C, ↑ LDL-C
	↑ Or no change in total cholesterol & triglycerides
Hormonal levels	↑ Testosterone & estradiol (with use of testosterone esters)
	↓ Testosterone (without use of testosterone esters or during withdrawal)
	↓ LH & FSH
Complete blood count	↑ RBC count, hemoglobin & hematocrit
Urine testing	
AAS:	Positive
Other drugs of abuse:	May be positive
Cardiac testing	
Electrocardiogram:	Left ventricular hypertrophy (seen in intensive weight trainers also)
Echocardiogram	Decreased ventricular ejection fraction, impaired diastolic function
Semen analysis	↓ Sperm count & motility, abnormal morphology

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *LDH* lactate dehydrogenase, *CK* creatine kinase, *GGT* gamma-glutamyltransferase, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *LH* luteinizing hormone, *FSH* follicle-stimulating hormone, *RBC* red blood cell

apparently increased prevalence of atherosclerotic disease in older AAS users (Kanayama et al. 2010b).

AAS also stimulate production of red blood cells, although the magnitude of this effect varies substantially across individuals. In our recent experience, we have seen several men who displayed hematocrits of 55–60 % while using AAS – placing them at increased risk for thrombotic or hemorrhagic complications.

Blood testosterone concentrations may be grossly elevated in patients who are administering exogenous testosterone, with serum concentrations typically several times the upper limit of normal (Kanayama et al. 2013). Conversely, testosterone concentrations may be grossly depressed in patients who are administering other types of AAS and hence inhibiting their own endogenous testosterone production. Testosterone levels may also remain depressed for months, and in rare cases even indefinitely, following AAS withdrawal (de Souza and Hallak 2011; Kanayama and Pope 2012).

37.3 AAS Dependence

Recent studies have increasingly documented that AAS can create a dependence syndrome, characterized by long-term use of these drugs, often for many years, and

frequently in spite of adverse effects (Kanayama et al. 2009). AAS dependence may be part of a larger pattern of dependence on appearance- and performance-enhancing drugs, involving other agents in addition to AAS, such as human growth hormone, insulin, and thermogenic agents such as clenbuterol, amphetamines, and thyroid hormones (Hildebrandt et al. 2011). As many as 30 % of men who use AAS may eventually develop such dependence syndromes (Kanayama et al. 2009), and thus there are likely some millions of cases worldwide.

We have suggested that AAS dependence may arise via three different pathways, any or all of which may contribute to the syndrome in a given individual (Fig. 37.1) (Kanayama et al. 2010a). First, there appears to be a "body-image" pathway, in which the individual becomes preoccupied that he will lose muscle size when he stops taking AAS and hence becomes reluctant to discontinue these drugs even for a short interval. Treatment for such symptoms, especially the extreme case of "muscle dysmorphia," can be performed with cognitive behavioral therapies or selective serotonin reuptake inhibitors (SSRIs). We discuss muscle dysmorphia in more detail below.

Second, use of exogenous AAS leads to suppression of the hypothalamic-pituitary-testicular (HPT) axis (de Souza and Hallak 2011; Tan and Scally 2009). Thus, when a man discontinues a course of AAS, especially if that course has been prolonged, he will likely experience hypogonadism, which in some cases may persist for months or even years after AAS are discontinued. Hypogonadism may be associated with loss of sex drive, fatigue, and occasionally serious depression; these symptoms may prompt users to quickly resume AAS in order to make the dysphoric feelings go away. This pathway to AAS dependence was first postulated more than 20 years ago (Kashkin and Kleber 1989) and has been increasingly acknowledged in recent years. Indeed, it now appears that protracted severe hypogonadism may be much more common in long-term AAS users than previously suspected and that indeed some users may develop irreversible hypogonadism, possibly attributable to direct toxic effects of long-term AAS exposure on the testis or on other components of the HPT axis (de Souza and Hallak 2011; Kanayama and Pope 2012). Therefore, in individuals displaying AAS-withdrawal hypogonadism and expressing a genuine desire to not resume AAS, it is desirable to institute aggressive endocrinological treatment with agents that stimulate the HPT axis in order to "jumpstart" natural endogenous testosterone production and thus reduce the individual's desire to resume illicit exogenous AAS (Tan and Scally 2009). Such treatment may include clomiphene to stimulate pituitary secretion of luteinizing hormone and follicle-stimulating hormone, together with human chorionic gonadotropin (HCG) to stimulate testicular production of testosterone and spermatozoa. Initially, the patient may also require temporary exogenous testosterone administration, typically using one of the several commercially available testosterone gels, in order to maintain adequate testosterone levels while waiting for clomiphene and/or HCG to stimulate resumption of endogenous function. In a typical treatment course of this nature, one would first taper off testosterone, then subsequently discontinue HCG, and then finally taper clomiphene, all while regularly monitoring testosterone levels (Tan and Scally 2009). Individuals still unable to

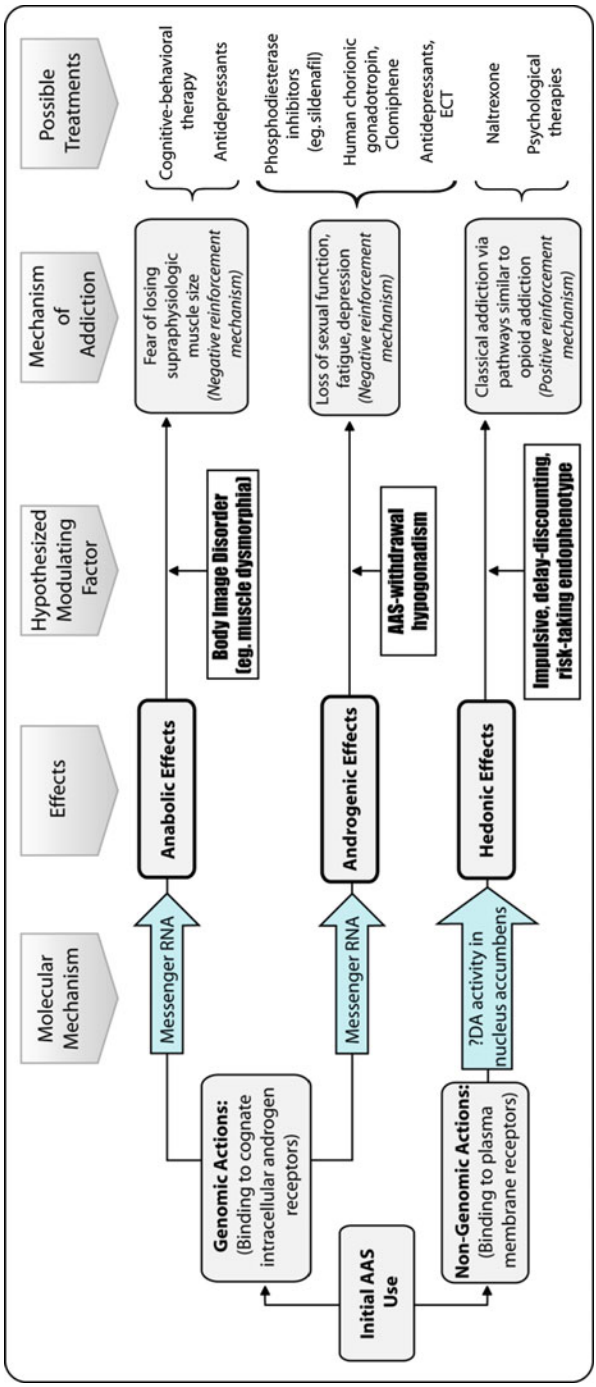

Fig. 37.1 Three potential pathways for the development of anabolic-androgenic steroid dependence and consequent possible treatment strategies (Adapted from Kanayama et al. 2010a)

maintain adequate testosterone levels on their own, even after several months of neuroendocrine treatment, may conceivably represent cases of irreversible hypogonadism attributable to a direct toxic effect of AAS and hence may require testosterone replacement indefinitely. Most psychiatric clinicians will likely wish to seek endocrinological consultation for these interventions.

Third, AAS may induce a dependence syndrome via a hedonic pathway, presumably mediated by receptor sites on cell membranes, rather than by classical anabolic or androgenic effects that are genomically mediated. Persuasive evidence for such a hedonic pathway arises from animal studies, which have shown that rats and mice display conditioned place preference for AAS and that male hamsters will self-administer AAS to the point of death (Wood 2008). Interestingly, AAS self-administration in hamsters can be blocked by administration of the opioid antagonist naltrexone (Wood 2008). A number of other clinical and preclinical studies have pointed to interactions between AAS and endogenous as well as exogenous opioids, thus suggesting that the hedonic pathway to AAS dependence may involve opioidergic mechanisms (Nyberg and Hallberg 2012; Wood 2008). One implication of this research is that human AAS dependence might respond, at least in part, to treatments empirically validated for opioid dependence, such as motivational therapies, contingency management, behavioral couples therapy, or behavioral family counseling. In the management of opioid dependence, some of these treatments have been successfully used in conjunction with naltrexone – raising the possibility that the addition of naltrexone might be effective in AAS dependence as well. However, these modalities have not yet been systematically tested in treatment of AAS dependence. We refer the reader to the full article from which Fig. 37.1 is taken (Kanayama et al. 2010a) for a detailed discussion of each of these three possible pathways to AAS dependence, together with details of potential treatment strategies.

37.4 AAS-Induced Hypomania and Mania

A substantial literature over the last 20 years has demonstrated that AAS produce hypomanic or manic syndromes in some individuals, sometimes accompanied by aggressive or violent behavior, and very rarely psychotic symptoms (Hall et al. 2005; Pope and Katz 2003). These effects are rare in individuals taking the equivalent of 300 mg of testosterone per week or less, but they appear to become progressively more common with higher doses, especially above 1,000 mg per week (Pope and Katz 2003). These syndromes were initially noted in field studies of illicit AAS users, and some investigators questioned whether the effects were actually due to AAS themselves, as opposed to expectational factors, personality variables, or subcultural influences. However, several studies have now demonstrated that such syndromes can develop even in normal volunteers taking supraphysiologic doses of AAS under placebo-controlled double-blind laboratory conditions (Pope and Katz 2003). Therefore, the mood-altering effects of AAS almost certainly have a biological basis, even though they can undoubtedly be

modified by contextual factors. Hypomanic and manic syndromes appear to be quite idiosyncratic, with a majority of AAS users displaying few such symptoms, even with high doses of AAS, but with occasional individuals showing severe symptoms, sometimes accompanied criminal violence (see below).

Little has been written about the treatment of such episodes beyond anecdotal reports. Thus, the best treatment recommendations would seem to include removal of the offending agent and temporary treatment, if necessary, with neuroleptics or other antimanic drugs. In general, it appears that manic or hypomanic episodes will remit quickly when AAS are stopped and that clinicians should then be alert for the onset of depressive symptoms associated with abrupt AAS withdrawal. If a patient reports a history of mood disorder prior to AAS use or continues to exhibit manic or psychotic symptoms for more than a few weeks after AAS are stopped, it would seem important to consider the possibility of an underlying major mood disorder independent of AAS.

37.5 AAS-Withdrawal Depression

As mentioned above, AAS-withdrawal hypogonadism has been increasingly recognized as an important problem in long-term AAS users. During AAS withdrawal, most men do not display marked depressive symptoms, even when their testosterone levels are grossly below the normal range. However, a small number of men develop pronounced depressive symptoms, sometimes accompanied by suicidal ideation and even completed suicide (Kanayama et al. 2010b). In mild cases, depressive symptoms may remit spontaneously as endogenous testosterone production gradually recovers. However, more severe or prolonged cases of depression may require both endocrinological interventions to restore HPT axis function, as described above, together with antidepressant treatment. Depression accompanying AAS withdrawal appears to respond well to SSRIs such as fluoxetine (Malone and Dimeff 1992). Antidepressant agents of this class may be particularly useful since they may also benefit muscle dysmorphia and other forms of body dysmorphic disorder that may accompany AAS use (Phillips et al. 2008).

37.6 Body-Image Disorders Associated with AAS Use

Recent years have seen increasing recognition of a form of body dysmorphic disorder called “muscle dysmorphia,” or “reverse anorexia nervosa,” in which the individual perceives himself to be small and frail, even though he is actually large and muscular (Rohman 2009). Men with muscle dysmorphia will often engage in compulsive weightlifting and bodybuilding, even to the exclusion of other activities that they enjoy. They also will frequently avoid situations in which their body will be seen by others, such as going to the beach or changing in a locker room, for fear that they look too small. Not surprisingly, such individuals may use AAS to “treat”

their preoccupation, but paradoxically, many describe worsening symptoms of muscle dysmorphia following initiation of AAS use. As mentioned earlier, muscle dysmorphia may contribute to AAS dependence, because individuals may become extremely anxious that they are losing muscle size or gaining fat after stopping AAS, and thus quickly resume use.

In individuals presenting with muscle dysmorphia and other similar concerns about body physique, the possibility of AAS use should always be considered and investigated. Successful treatment of the underlying body-image disorder may be helpful for deterring future AAS use – although individuals with muscle dysmorphia may be reluctant to admit that they have a condition requiring treatment, as is often the case with other forms of body dysmorphic disorder. We are not aware of systematic studies of treatment of muscle dysmorphia per se, but it seems reasonable to follow general principles of treatment of other forms of body dysmorphic disorder, relying on cognitive behavioral therapy and pharmacological interventions such as SSRIs – modalities of demonstrated efficacy in body dysmorphic disorder generically (Phillips et al. 2008).

37.7 Co-occurring Substance Use Disorders

A growing literature has demonstrated that polypharmacy is widespread among AAS users. These individuals may use a variety of other performance- and image-enhancing drugs, such as human growth hormone, insulin, and agents for fat loss, and they frequently also display abuse of, or dependence on, classical drugs of abuse such as cannabis, amphetamines, cocaine, and opioids (Dodge and Hoagland 2011; Hildebrandt et al. 2011; Kanayama and Pope 2012; Skarberg et al. 2009). In particular, the association of AAS use with opioid use may in part reflect similarities between these classes of drugs in their reward mechanisms, as discussed earlier (Nyberg and Hallberg 2012; Wood 2008). In our experience, concomitant opioid abuse or dependence is particularly common in North America, where we have evaluated many AAS users who were first introduced to oral opioids or intravenous opioid agonist-antagonists such as nalbuphine and then progressed to intravenous use of classical opioids such as morphine and heroin. We are aware of several cases in which such individuals later died from inadvertent overdoses of intravenous opioids. In Europe, a specific link between AAS and opioid use appears less prominent, with AAS use commonly associated with other abuse of drugs such as cocaine, cannabis, and amphetamines (Garevik and Rane 2010; Skarberg et al. 2009).

It follows from these observations that clinicians should assess history of classical drug abuse in all individuals presenting with AAS use and conversely should consider the possibility of AAS use in individuals presenting with classical drug abuse. In either case, classical substance abuse or dependence in current or former AAS users may well itself require treatment; the reader is referred to the corresponding chapters in this volume regarding principles for such treatment.

37.8 Medical Conditions Associated with AAS Use

Long-term use of AAS may be associated with a variety of medical complications, the full extent of which is only gradually becoming appreciated. One reason for our still-limited knowledge of these effects, mentioned earlier, is that AAS use did not become widespread in the general population until the 1980s. Thus, a majority of the world's AAS users are still young and have yet to pass through the age of risk for medical complications of long-term use. To cite an analogy proposed in our earlier publications (Kanayama et al. 2008), imagine that widespread cigarette smoking did not exist until the 1980s and that the great majority of the world's cigarette smokers were still below age 50 today. In that scenario, we would have only a limited recognition of the potential long-term risks of cigarette smoking and might substantially underestimate the true amount of morbidity and mortality that would ultimately occur.

An analogous situation may exist with regard to AAS. Recent years have seen growing evidence that AAS produce adverse cardiovascular effects (e.g., cardiomyopathy, myocardial infarction, cerebrovascular accidents), protracted neuroendocrine disruption (as discussed above), and effects on other organ systems (e.g., focal segmental glomerulonephritis) (Kanayama and Pope 2012). It is our impression that these adverse consequences are more frequent and more serious than most authorities (including ourselves) would have anticipated even a few years ago. Mounting evidence also suggests that supraphysiologic concentrations of AAS may produce apoptotic effects in a variety of cell types, including the myocardial and skeletal muscle cells, epithelial cells, Leydig cells, and neuronal cells (Kanayama et al. 2013). The finding of neuronal apoptosis raises the specter of potentially irreversible cognitive deficits in AAS users – a phenomenon that we have already tentatively observed in a pilot study (Kanayama et al. 2013).

It follows that aging AAS users may increasingly come to clinical attention as a result of various medical or neurological effects. Thus, substance-abuse professionals may receive referrals of such patients from medical clinicians, many of whom may themselves be unfamiliar with illicit AAS use. Such patients may need to discontinue AAS immediately as a result of medical dangers. Many of these patients may never have previously disclosed their AAS use to any clinician and may be very uncomfortable with the idea of entering treatment and discontinuing AAS. Prompt, knowledgeable, and sympathetic intervention, addressing all of the three AAS-dependence pathways postulated above, may be required to achieve a good outcome.

37.9 AAS in Forensic Situations

AAS users may occasionally come to clinical attention through the courts as a result of violent or criminal behavior. Specifically, a number of papers have described individuals, often with no prior history of psychiatric disorder, violence, or criminal behavior, who became uncharacteristically violent, and sometimes committed murder while intoxicated with AAS (Hall et al. 2005; Kanayama et al. 2010b;

Pope and Katz 2003). In such cases, AAS are not necessarily the proximal trigger to violence; the direction of causality may sometimes be reversed, in that some individuals may deliberately ingest AAS in preparation for committing a crime (Lundholm et al. 2010). A recent example of such a case was Anders Breivik, convicted of killing 77 Norwegian civilians in the summer of 2011. In his extensive manifesto, Breivik details his systematic use of AAS, which he ordered through the Internet, in preparation for his terrorist attacks (Kanayama and Pope 2012).

In some cases of criminal violence, the role of AAS use may be missed because the possibility is never considered. However, AAS use should be suspected in any usually muscular man apprehended for violent behavior, especially if it appears that this violence is not characteristic of his usual personality. The clinician's index of suspicion should be particularly raised if such a man rapidly develops vegetative symptoms of depression after being incarcerated, but then improves a few weeks or months later. This pattern may indicate AAS withdrawal, precipitated by the abrupt discontinuation of AAS following incarceration, with a gradual remission of depressive symptoms as suppressed hypothalamic-pituitary-testicular function gradually returns to normal. Of course, this pattern of biological depression must be distinguished from the situational depression associated with incarceration itself.

In cases where AAS use is acknowledged by the defendant and appears to have been a clear precipitant of criminal behavior, forensic clinicians may be asked to offer an opinion that the defendant exhibited "involuntary intoxication" or "diminished capacity" from AAS. The legal aspects of this defense are beyond the scope of this chapter. However, it seems clear that if an individual is released and placed on probation after a crime believed associated with AAS, it may be wise to require random, unannounced, observed urine tests for AAS to ensure that he does not resume these drugs.

37.10 Conclusion

Of the various major forms of substance abuse and dependence described in this volume, AAS abuse and dependence may be the least familiar to the average clinician. However, the frequency of AAS abuse and dependence, together with the various medical and psychiatric syndromes associated with it, is now beginning to be better recognized. Greater awareness of this problem among clinicians may lead to the detection of many more cases, and a better understanding of how best to treat them.

37.10.1 Key Points

- Anabolic-androgenic steroid (AAS) use must be approached differently from other forms of substance abuse, because AAS do not produce an immediate reward or "high" in the manner of conventional drugs of abuse, and are linked to body dysmorphic disorder.

- AAS users rarely see their drug use as pathological, rarely seek treatment, and may have contempt for physicians.
- AAS users often display a history of abuse of or dependence upon other drugs, especially opioids.
- Some individuals experience hypomanic or manic symptoms during AAS exposure and depressive symptoms during AAS withdrawal.
- AAS may produce a well-documented dependence syndrome, for which an animal model exists. This dependence syndrome may arise through several pathways, including a "body-image" pathway, a neuroendocrine pathway, and a hedonic pathway, each of which may dictate specific treatment interventions.

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Prescription Drug Abuse: Risks and Prevention

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Contents

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Abstract

Abuse of and dependence on prescription drugs is an increasing problem and is closely related to the increasing use of prescription drugs worldwide. The problem of prescription drug abuse includes both weak and strong opioids for pain management; sedating drugs like benzodiazepines, barbiturates, and newer hypnotics; and stimulant drugs used for the treatment of narcolepsy and ADHD. Several other prescription drugs also have the potential for abuse. In this chapter prescription drug abuse is set in an historical context. The concept of prescription drug abuse is discussed and the types of drugs that are abused are reviewed. The special considerations that need to be upheld when diagnosing and understanding prescription drug abuse are highlighted. The chapter also contains information on the epidemiology of prescription drug abuse. As prescription drugs are effective drugs that are needed for the treatment of serious diseases, special responsibility for the prevention of the problem of prescription drug abuse is placed on the prescribing doctor. Lastly special considerations in treating prescription drug abuse and especially long-term benzodiazepine use are reviewed.

38.1 Introduction

For as long as we have had medicinal drugs, we have had abuse of these drugs. Similarly, drugs of abuse have long been used for their therapeutic potential, real or perceived. Cannabis, opium and its derivatives, cocaine, and barbiturates are good examples. Much of the legislation requiring prescription by doctors was brought in to prevent the abuse of medicinal drugs and narcotics and even alcohol. At the time there was a belief that having doctors administer the use of these drugs would prevent some of the problems connected with them. This is, for good reason, still a widely held belief. But as we shall see in the following text, requiring prescription of these drugs does not solve the problem of abuse. Nonetheless it may be the best system available for the distribution of these potentially harmful helpers. It does, however, place a great deal of responsibility on the professionals entrusted with this task.

Historically there are many examples of drugs of abuse being used as medicines. The use of cannabis for medical purposes has its roots in the ancient civilizations of China, Egypt, and Greece. The use of opiates for both medical and recreational purposes went hand in hand in old cultures in the Middle and Far East. This was also probably true for South American use of cocaine and was certainly true when the drug came to Europe in the second half of the nineteenth century. Sigmund Freud wrote four papers on the medical use of cocaine (Freud 1884) and developed an addiction himself (Cohen 2011). Others developed the first local anesthetics from it. When the first effective sleeping agents, barbiturates, were introduced, the road to abuse was a short one, and for decades, the problem was considerable in the Western world.

Even today the boundaries may seem vague. Just as Freud thought that cocaine could be a cure for morphine addiction, so heroin was introduced for the same reason. In the 1890s many believed that heroin was not an addictive drug itself. They could not have been more wrong! Some 70 years later Dole and Nyswander introduced the concept of opiate maintenance treatment using long-acting opioids (Dole and Nyswander 1967), thus sparking one of the greatest treatment options for heroin addiction with several hundred thousand patients being treated worldwide. This is obviously a great treatment opportunity but nevertheless is still considered controversial in many countries. The story goes full circle with the introduction of heroin as a substitution drug to be used for difficult-to-reach opiate addicts, an indication that it is not the addiction per se that we seek to treat, but the adverse effects of the addiction lifestyle, namely, criminality and social marginalization.

The boundaries are also unclear with the increasing use of medicinal drugs for recreational purposes. These include drugs such as newer opioids, like pregabalin (Lyrica), but also the older benzodiazepine sedatives and hypnotics and benzodiazepine-like hypnotics. At the same time, there is a push toward the medical use of drugs normally used for recreational purposes. Medical marijuana has a growing following worldwide and this has formed the basis for challenging the legislation concerning cannabis, pushed both by cannabis liberalists and also by more scientifically oriented researchers who see the paradox in potential therapeutics being outlawed. Other drugs have also been "pushed" by "drug activists": MDMA for the treatment of depression and psychedelics for the treatment of other psychiatric conditions. Much of this interest appears to be fueled by special interest groups with an agenda for liberalization and may be a romantic view of "mind-expanding drugs." This may be best illustrated by the interest in the use of psychedelics in the treatment of addiction in order to "induce transcendental experiences" as part of a cure for addiction.

Two issues should be kept in mind. Firstly, requirements for efficacy and evidence should be just as strict toward drugs derived from narcotics as for any medicinal drug if they are to be used therapeutically. The research concerning the use of cannabinoids in medicine is a good example of this – showing that there is evidence for the efficacy of cannabinoids. Secondly, the abuse potential of any drug that is to be put on the market should be clarified as a prerequisite of any registration process. Guidelines for such testing exist (FDA 2010). But many of these drugs were marketed long before modern requirements to investigate their abuse potential were in place. And even with careful testing, the real abuse potential of many drugs may not be fully recognized. This is because preclinical and pre-marketing investigations, however meticulous, are not able to reveal a drug's true abuse potential. They are often tested on smaller, selected (non-abuser) populations under strictly controlled conditions, which do not allow for spurious use. It will often take years after a drug has come on the market before its true abuse potential becomes clear. Post-marketing surveillance is one of the few ways of picking up abuse of drugs; many drugs are not fully recognized for their abuse potential until they have been on the market for many years (Arfken and Cicero 2003).

Novel synthetic cannabinoids were developed as medicinal drugs. Although they have some therapeutic value, their real popularity has been won by recreational use. Their potency makes them easy to distribute. And the ever-increasing number of new varieties, partly synthesized to avoid legal persecution, reminds us of Alexander Shulgin's efforts in the ecstasy field (Shulgin and Shulgin 1991). These drugs again illustrate how drugs with medical potential are brought into recreational use.

Even though there are many drugs that have abuse potential, they obviously also have a therapeutic benefit. So if abuse potential is discovered, it is most often not a question of taking the drug off the market. It can be scheduled with restrictions on its use. It is always a question of weighing the risks against the benefits. If the risks are perceived to be greater than the benefits, action should be taken. Ultimately this could mean withdrawing the market authorization of a drug, but often more modest actions will serve the purpose.

A surprising number of medicinal drugs, which later prove to have an abuse potential, have been marketed as safe from the danger of abuse. This suggests that marketers are well aware of this danger and want to reassure us, even if their claims are not always true. Abuse of medicinal drugs is an adverse effect best avoided, but not at any cost. When review papers on the use of cannabis reveal that it is an effective drug, but suggest it should not be used because of its abuse potential (Tramer et al. 2001), we must again try to weigh the risks and the benefits. If a terminal cancer patient, a chronic Parkinson patient, or even a chronic drug addict were to feel some pleasure from the drugs given to them therapeutically, it does not automatically shift the weight away from use of the drug. It is something to be taken into consideration, but not something that should necessarily prohibit its use.

This backdrop may be useful to keep in mind when encountering prescription drug abuse, be it as a doctor worried about prescribing drugs that could be used for reasons other than therapeutic, a therapist encountering a patient with abuse or dependence problems because of these drugs, or those contemplating using known drugs of abuse for the benefit of seriously ill patients.

38.2 Prescription Drugs of Abuse

This chapter will cover the most important groups and compounds. Sedatives and hypnotics will be covered in more detail here because they are not elaborated on elsewhere in this textbook.

38.2.1 Sedative Drugs

This group of drugs covers many different compounds (Table 38.1). These mainly belong to four subgroups: benzodiazepines, z-hypnotics, barbiturates, and barbiturate-like substances. Common to all of them is that they have receptor sites on the gamma-aminobutyric acid (GABA) receptor, subtype A. GABA is the main inhibitory neurotransmitter in CNS and is widespread throughout the CNS.

Table 38.1 Some commonly used sedatives marketed in many countries. Not all drugs will be marketed in all countries

	Compound (generic name)	Main use	Mean usual dose main use (mg)	Mean terminal half-life (h)	Abuse potential
Benzodiazepines	Alprazolam	Anxiolytic	1	12	***
	Bromazepam	Anxiolytic	9	16	**
	Lorazepam	Anxiolytic	4	12	***
	Oxazepam	Anxiolytic	30	10	*
	Chlordiazepoxide	Anxiolytic	30	27	**
	Clobazam	Anxiolytic	30	18	**
	Diazepam	Anxiolytic	5	40	**
	Lorazepam	Hypnotic	1	12	***
	Temazepam	Hypnotic	15	14	**
	Flunitrazepam	Hypnotic	1	25	***
	Nitrazepam	Hypnotic	5	28	**
	Flurazepam	Hypnotic	15	60	***
	Clonazepam	Antiepileptic	4	36	***
Benzodiazepine-like hypnotics	Zaleplon	Hypnotic	10	1.5	*
	Zopiclone	Hypnotic	7,5	4.5	**
	Eszopiclone	Hypnotic	6	6	**
	Zolpidem	Hypnotic	5	2.5	**
Barbiturates	Barbital	Antiepileptic	750	30	***
	Fenobarbital	Antiepileptic	200	80	***
Barbiturate-like drugs	Chlomethiazole	Muscle relaxant	600	6	**
	Meprobamate	Muscle relaxant	200	10	***
	Methaqualone	Muscle relaxant	150	74	***
	Chlormezanone	Muscle relaxant	200	40	**
	Orphenadrine	Muscle relaxant	100	16	**
	Chlorzoxazone	Muscle relaxant	750	1	**
	Carisoprodol	Muscle relaxant	700	2	**

Different sources of data indicate that the these drugs *may be abused; **have a moderate abuse potential; or ***are drugs with a high abuse potential

The $GABA_A$ receptor complex is a ligand-gated ion channel. This transmembrane chloride channel is a pentamere with several different combinations of α (six subtypes), β (three subtypes), or γ (three subtypes) subunits and some other possible variants. It is to a large extent the α-subunit configuration that determines a drug's abuse potential (Tan et al. 2011; Ator 2005). While the barbiturates and barbiturate-like drugs can influence the receptor in the absence of GABA,

benzodiazepines and the benzodiazepine-like z-hypnotics are dependent on the presence of GABA in order for the receptor to perform its action. The consequence is that while barbiturates and barbiturate-like drugs are more dangerous and may more easily be overdosed, benzodiazepines and benzodiazepine-like drugs have a ceiling effect and thus a broad therapeutic window of use. The literature gives few, if any, examples of overdose on benzodiazepines alone in otherwise healthy individuals.

It is thus safe to say that when benzodiazepines were introduced in the end of the 1950s and in increasing numbers in the 1960s and 1970s, this was viewed as a better and safer alternative to the barbiturates that had caused so many deaths and so much dependence (Lader 1991). But, as many other times, the true abuse potential of the drug was not revealed until later, and only in the late 1960s and early 1970s did the abuse of benzodiazepines become recognized.

Benzodiazepines are basically the same no matter what their main indication is. It is often arbitrary what indication the market authorization is filed for, depending on whether there are fewer or more drugs in a group. It is most often a question of the dosage regardless of whether a benzodiazepine is used as an anxiolytic, a hypnotic, or an antiepileptic drug. What differs between the compounds is their potency and their pharmacokinetics. Table 38.1 shows this through the dosing and the terminal elimination half-life. Concerning dosing, it must be remembered that dosing in this table (and in much of the literature) is for the main use the drug is registered for. Taking diazepam as an example, doses would be 5–10 mg for anxiety but 10–20 mg for sleep. The daily doses however may reach as much as 15–20 mg for anxiety treatment as the dose if often repeated, but there is no such repetition for hypnotics. So equipotency for benzodiazepines is not a simple term. However, some are more potent than others (alprazolam, lorazepam, flunitrazepam, and clonazepam) and thus more attractive among abusers (Hallfors and Saxe 1993; Ator et al. 2005; Griffiths and Johnson 2005), partly because clinicians have a tendency to underestimate the potency differences and prescribe high-potency benzodiazepines in relatively higher doses. The terminal elimination half-life is another parameter which varies between the benzodiazepines. It must however be remembered that owing to the phenomenon of acute tolerance (tolerance occurring within the same dosing), terminal elimination half-life is not a good parameter for judging the time of effect for benzodiazepines. But the relative duration of action between the different benzodiazepines is roughly judged by this parameter. And a short duration of action often implies a short time between intake and effect, a parameter important for the reinforcing effects of a drug. Again we see alprazolam, lorazepam, flunitrazepam, and clonazepam scoring highly on this parameter.

Z-hypnotics (zaleplon, zopiclone, eszopiclone, and zolpidem) are not benzodiazepines in their chemical structure. When introduced, their manufacturers wanted to have them introduced as "benzodiazepine-free hypnotics." However, their similarities to benzodiazepines in pharmacological effects are striking and there is no longer doubt

that they can be abused. These drugs probably have a lesser capacity to relieve anxiety and the role of anxiety in a drug's abuse potential should not be underestimated. It is thus probably true to state that the abuse potential of these drugs may be lower than for benzodiazepines, but the difference is likely to be marginal. We still see that zolpidem is a very popular drug of abuse in many countries. A distinct metal taste following the intake of zopiclone (also after i.v. intake) is probably preventive for abuse. Despite many claims to the contrary, eszopiclone has no advantages over zopiclone and probably none over benzodiazepines in terms of abuse potential. These drugs can be and are abused (Jaffe et al. 2004; Hajak et al. 2003).

Benzodiazepines are hugely popular among injecting drug addicts. Heroin users use them to prolong their intoxication and prevent withdrawal (Ross and Darke 2000). This may also contribute significantly to overdose deaths (Clausen et al. 2009). Abusers of stimulants use them to land from binges or runs.

Barbiturates and barbiturate-like drugs are much less abused today than they were before. That does not mean that they cannot be abused! Many of these drugs are compounds that have taught us what prescription drug abuse is, like methaqualone (Quaalude®). Their high lipid solubility and resulting potential to cross the blood-brain barrier quickly and their unlimited effect (ever-increasing effects with higher doses and no ceiling effect, even if marked tolerance triggered massive dose escalations) made them very popular as drugs of abuse. When this was acknowledged, heavy restrictions were put on their prescribing and these drugs were withdrawn in many countries, but they are still on the market in many others.

It is a point of discussion whether or not buspirone should be listed here. We have opted not to do so because of the low abuse potential shown for this drug in several studies. This is not to say that it cannot be abused in some situations or by some patients.

38.2.2 Analgesics

The mechanism of action and other pharmacological points concerning opioid analgesics, including those which are prescribed, are similar to that described elsewhere in this book. There are at least two different groups of prescription opioid abusers. Firstly, we have the pain patient who has aberrant use of his or her medication (Turk et al. 2008). Who the patients at risk are seems to be difficult to predict. And then we have the abusers without a prescription. This group includes anyone from the teenager who accesses a relative's pain medication to the marginalized heroin abuser adding prescription opioids to his or her abuse. Common for all of these are the dangers related to abuse, dependence, and overdose. For further characterization of user groups, see below. The nonmedical use of prescription opioids is a modern-day epidemic with an estimated use in the United States of around 4 % of the population (UNODC 2012) (Table 38.2).

Table 38.2 Some commonly used opioids marketed in many countries. Not all drugs will be marketed in all countries

Compound	Main use	Mean terminal half-life (h)	Abuse potential	Comment
Morphine	Pain relief	2–3	***	
Ethylmorphine	Cough suppression	?	**	
Codeine	Pain relief	3–4	*	(10 % metabolized to morphine by CYP2D6)
Fentanyl	Anesthesia	1–6	***	Also much used as a transdermal patch
Hydrocodone	Pain relief	4–6	**	
Oxycodone	Pain relief	3–5	**	
Oxymorphone	Pain relief	1–2	**	
Dextropropoxyphene	Pain relief	8–24	***	
Hydromorphone	Pain relief	2–3	**	
Meperidine/ pethidine	Pain relief	3–5	**	
Diphenoxylate	Constipating drug	12–14	*	
Methadone	Substitution in opioid dependence	6–8	**	High doses make once-daily intake possible
Buprenorphine	Substitution in opioid dependence	4–6	**	Strong binding (covalent) to receptor makes once-daily intake possible

Different sources of data indicate that the these drugs *may be abused; **have a moderate abuse potential; or ***are drugs with a high abuse potential; ? denotes an unknown abuse potential

38.2.3 Central Stimulants

During recent years there has been an enormous increase in the prescribing of central stimulating drugs for treating attention deficit and hyperactivity disorder (ADHD). Using central stimulants to treat ADHD is an effective treatment in children (Bloch et al. 2009) and probably also in adults (Wilens et al. 2002), but not all these drugs are used as prescribed; some are also abused. This is partly true because patients with ADHD have an extra vulnerability to getting involved in drug use (Groenman et al. 2013). The drugs can be abused by saving a whole week's worth of pills for a simultaneous intake to get a stimulant high or by selling the drugs to friends or on the black market. A typical therapeutic use of methylphenidate would involve using 10–30 mg, but 50–150 mg would be common in abuse. It is debatable whether or not buproprione should be listed here. We have opted not to do so because of the low abuse potential of this drug shown by several studies. This is not to say that it cannot be abused in some situations or by some patients.

Abuse of central stimulants includes using them as cognitive enhancers. This means otherwise healthy people taking the drugs in order to optimize their

Table 38.3 Some commonly used central stimulating drugs marketed in many countries. Not all drugs will be marketed in all countries

Compound	Main use	Mean usual dose main use (mg)	Mean terminal half-life (h)	Abuse potential
Methylphenidate	ADHD and narcolepsy	20–30	2–3; 7–12 for extended release	**
Amphetamine	ADHD and narcolepsy	20	13	***
Dextroamphetamine	ADHD and narcolepsy	20	10	***
Ephedrine	Cough medicine	20–50	3–6	*
Diet pills	Weight loss	Varying	Varying	Varying
Caffeine	Narcolepsy and in combination for migraine	Varying	Varying	Varying
Melanotan	Illegal tanning product	10–30	1–2	?

Different sources of data indicate that the these drugs *may be abused; **have a moderate abuse potential; or ***are drugs with a high abuse potential; ? denotes an unknown abuse potential

cognitive abilities, such as using them to increase school performance or to stay awake and work for prolonged periods, be it as a student, soldiers in the field, or a truck driver with long shifts. Different surveys show varying degrees of use, but quite a few students report having tried them to increase performance, with varying results (Ragan et al. 2013). There is more solid evidence that they can improve cognitive performance better in periods of prolonged wakefulness, a fact that the world's many coffee drinkers can verify. Research in the combat field has, however, shown that the use of stronger central stimulants may not be optimal. In this field there is interest in a wide variety of drugs stimulating the noradrenergic, serotonergic, and glutaminergic receptor systems. This field is pushed forward by an interest in finding effective treatments for the cognitively impaired, such as patients with Alzheimer's disease.

It has been claimed that any diet pill that works includes central stimulants and that any diet pill that does not include central stimulants does not work. This is too simplistic a view and does not take into account the many different approaches diet pills have used, but it certainly captures the point that dieting agents, for many years, included central stimulants and that this appeared to be efficient (Table 38.3).

38.2.4 Other Drugs

Virtually any drug can be abused. No complete list will ever be compiled. As prescribers we always need to work with others to produce early warning systems and to remain up-to-date on the possible dangers of prescribing different drugs. We must remember that abuse potential is often not revealed until a drug has been on the market for a very long time (Table 38.4).

Table 38.4 Miscellaneous drugs that have been reported abused. Not all drugs will be marketed in all countries

Compound	Main use	Abuse potential	Comment
Marinol and other synthetic cannabinoids	Pain and muscle spasms in MS patients	***	Being a synthetic cannabinoid with very high potency, it has a high abuse potential
Sativex (cannabis extract)	Pain and muscle spasms in MS patients	*	Abuse potential as with other cannabis products
Pregabalin	Antiepileptic	**	Increasing number of case reports point to the abuse potential of this GABA analogue
Ketamine	Anesthetic	**	This anesthetic is an antagonist to the glutamatergic NMDA receptor giving vivid hallucinations as one of its main effects
Quetiapine	Antipsychotic	*	Increasing number of case reports point to the abuse potential of this antipsychotic drug
Xyrem	GHB treatment of alcohol dependence and withdrawal	***	This GHB product can of course be abused as GHB
Lioresal	$GABA_B$-agonist	*	This centrally acting muscle relaxant can possibly be abused in higher doses, but the euphoric and psychomotor effects are weak

Different sources of data indicate that the these drugs *may be abused; **have a moderate abuse potential; or ***are drugs with a high abuse potential

38.3 Terminology and Diagnosis

Most use of prescription drugs is legitimate and therapeutically wise. The overwhelming majority of those who receive a prescription for analgesics or for hypnotics or sedatives use these drugs for a limited period to get through a time of pain, insomnia, or life stress. It is important to underline this because even if we have, for too long, overlooked the problem of abuse of these drugs, we must not go to the other extreme and view all use of these drugs as problematic.

However, problems can and do arise. People can use too much. Some individuals can increase their doses to high amounts. Others can use them for too long, after their original problem is over, in order to avoid the discomforts of discontinuation and withdrawal. The drugs can be taken for the wrong reasons. They are not meant to be used recreationally or as part of an addiction. And some people mix different drugs. This can be done for several reasons, but increases the addictive potential of the drugs and also increases the chances of intoxication, often lethal.

In this context of numerous patterns of drug use, some stand out as more archetypical.

38.3.1 Pseudo Therapeutic Long-Term Use

Sedating drugs are meant for short-term use only. The manufacturers, authorities, and society guidelines say that the drugs should be used only for 3–4 weeks. Still many patients continue to use the drugs for longer. This group of patients may cause concern at the doctor's office because of discussions about the re-prescribing of the drugs. Many patients feel that their honesty is being questioned and many doctors feel that they are being "forced" into prescribing for longer than necessary. These patients, however, are not true abusers. They certainly use the drugs for longer than intended, but seldom at high doses, most often at lower doses than prescribed, and they seldom increase their doses. These users are often termed quasi-therapeutic long-term users (Griffiths and Weerts 1997). They are mentioned here because they are quite prevalent and clearly violate recommendations, but may not represent a true problem.

38.3.2 Self-Medicating Pain/Anxiety/Insomnia Patients

Patients with anxiety disorders, but also patients with other psychiatric disorders, may use different prescription drugs to self-medicate or treat their symptoms (McCabe et al. 2009). It is important to acknowledge that anxiety disorders, major depression, PTSD, personality disorders, and pain conditions may lead to overuse of prescription drugs. The possibility of abuse should not stop the doctor from introducing effective and necessary treatment, but the dangers of overuse should be kept in mind. Even when drugs are used as prescribed, the patient may encounter problems such as tolerance, abstinence, abuse, and dependence (see below).

38.3.3 True Prescription Drug Abuser

Some patients can be labeled true prescription drug abusers. These are patients with no or marginal reasons to use these drugs, who still keep using the drugs, often in increasing dosages. They are involved in drug-seeking behaviors such as doctor shopping, prescription forging, and diversion of drugs prescribed to others. The doctor should be aware of these individuals, even though it is not a large group. These patients resemble the next group.

38.3.4 Polydrug Abuse

Many users of heroine or central stimulants use prescription opioids as part of their addiction (Gambi et al. 1999). Benzodiazepines are used to increase the high but also to postpone abstinence in heroin users or to end a binge in users of central stimulants. When such combination use occurs, it is often labeled as polydrug abuse, but it can be argued that it in fact represents a kind of self-medication in

drug abusers who have a main drug problem, be it heroin or central stimulants. This distinction may be important for treatment choices.

The typical patterns of drug use mentioned above may or may not fulfill the criteria for abuse or dependence on drugs. They are not, however, formal diagnoses. The current diagnostic systems define harmful use or abuse and dependence on drugs in the following manner (Table 38.5).

But these diagnoses may not be adequate for prescription drug problems (Kan et al. 2001). Some have thought that these diagnoses are too normative or even stigmatizing, as patients who only have done what the doctor has ordered would be labeled as abusers or dependants. There have been suggestions of using another nomenclature for prescription drugs than for other drugs. This has particularly been advocated in the pain management community, with the increasing use of opioids for nonmalignant pain. It has been argued that three new categories should be introduced (Ballantyne and LaForge 2007): problematic use of prescription drugs, addiction to prescription drugs, and *iatrogenic pseudo-addiction*. It is difficult to see how the two first categories differ substantially from abuse and dependence as defined above. The latter category, however, acknowledges the fact that some aberrant use may be due to suboptimal treatment of the primary condition (especially pain treatment). This kind of inappropriate use is characterized by uncontrolled prescribing of short-acting opioids or low doses of long-acting opioids. In both these cases, patients experience a slowing effect during the period between two doses. This may cause the patient to ask for larger and/or more frequent doses, which could lead to misconceptions of problematic opioid use and break down the trust between the patient and the physician. This leads to a difficult treatment situation which may gradually worsen. In such cases we are talking about iatrogenic abuse. Pain doctors have termed this pseudo-addiction. This terminology has been questioned by some (Manchikanti et al. 2012), who see this way of thinking as an excuse for the large increases observed in opioid abuse.

38.4 Epidemiology of Prescription Drug Abuse

It has been claimed that one third of the world's drug problems stem from alcohol, one third from narcotic drugs, and one third from prescription drugs. Even if this statement highlights the importance of prescription drug abuse, it is obviously too simplistic at least in underestimating problems related to alcohol. Neither does it account for the differences between these problems. But it is difficult to get more accurate figures. Information about aberrant use of substances is not easily available. Responders tend not to answer questions truthfully. Some are reluctant to admit breaking the law. There may also be over-reporting; among the younger population some will be reluctant to admit that they are the only ones who have not tried drugs. And often the people of most interest are not available for answers; they may be imprisoned or in treatment. Some of those you would most like to respond to a survey never open their mailbox or do not even have an address. On the other hand, if you choose to do your research in a prison or a treatment institution,

Table 38.5 Diagnostic criteria according to ICD-10 and DSM-IV for harmful use/abuse and dependence. These criteria apply to prescription drug abuse as for other substances

	ICD-10	DSM-IV
Harmful use/abuse	The diagnosis requires that actual damage should have been caused to the mental or physical health of the user	Substance abuse is defined as a maladaptive pattern of substance use leading to clinically significant impairment or distress as manifested by one (or more) of the following, occurring within a 12-month period
	Harmful patterns of use are often criticized by others and frequently associated with adverse social consequences of various kinds. The fact that a pattern of use or a particular substance is disapproved of by another person or by the culture, or may have led to socially negative consequences such as arrest or marital arguments is not in itself evidence of harmful use	Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (such as repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; or neglect of children or household)
	Acute intoxication or "hangover" is not in itself sufficient evidence of the damage to health required for coding harmful use	Recurrent substance use in situations in which it is physically hazardous (such as driving an automobile or operating a machine when impaired by substance use)
	Harmful use should not be diagnosed if dependence syndrome, a psychotic disorder, or another specific form of drug- or alcohol-related disorder is present	Recurrent substance-related legal problems (such as arrests for substance related disorderly conduct)
		Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (for example, arguments with spouse about consequences of intoxication and physical fights)
Dependency	A definite diagnosis of dependence should usually be made only if three or more of the following have been present together at some time during the previous year	
	(1) A strong desire or sense of compulsion to take the substance	
	(2) Difficulties in controlling substance-taking behavior in terms of its onset, termination, or levels of use	
	(3) A physiological withdrawal state when substance use has ceased or have been reduced, as evidenced by: the characteristic withdrawal syndrome for the substance; or use of the same (or closely related) substance with the intention of relieving or avoiding withdrawal symptoms	
	(4) Evidence of tolerance, such that increased doses of the psychoactive substance are required in order to achieve effects originally produced by lower doses (clear examples of this are found in alcohol- and opiate-dependent individuals who may take daily doses sufficient to incapacitate or kill non-tolerant users)	
	(5) Progressive neglect of alternative pleasures or interests because of psychoactive substance use, increased amount of time necessary to obtain or take the substance or to recover from its effects	
	(6) Persisting with substance use despite clear evidence of overtly harmful consequences, such as harm to the liver through excessive drinking, depressive mood states consequent to periods of heavy substance use, or drug-related impairment of cognitive functioning; efforts should be made to determine that the user was actually, or could be expected to be, aware of the nature and extent of the harm	

you will face the problem of selection bias. Not all abusers or dependants will be under treatment or imprisoned. The take-home message is that to study the epidemiology of abuse, you need to draw on a variety of sources to aggregate comprehensive data. This is no less true for prescription drug abuse.

There are two principle types of information that we aim to gather from epidemiological studies. The first is to look for signals of abuse in drugs not previously recognized as drugs of abuse. This is pharmacological research. Case reports and case series often give the first signals of such abuse potential (Arfken and Cicero 2003; Hajak et al. 2003). These signals must be followed up by more systematic and broader investigations. This is done both to substantiate a signal of a drug having an abuse potential and to investigate the extent of abuse. This kind of information is essential for grasping the size of the problem and how to cope with it. This is epidemiological research. The different sources of data below may serve as providers of both types of information.

38.4.1 Monitoring Patients or Populations

38.4.1.1 Population Surveys

Surveys have shown us that non-prescribed use of prescription drugs is quite common. The National Comorbidity Survey showed that more than 7 % of adults reported having used non-prescribed sedatives (Goodwin and Hasin 2002). Being male, being older, having a parent who has done the same, and reporting more psychiatric symptoms increased the risk (Clark et al. 2004; Brunette et al. 2003). From other studies we know that people with alcohol or drug-use problems have a higher risk of abusing prescription drugs (Longo and Johnson 2000). A survey, also from the United States, showed that during the previous month, around 2 % of the total population (≈6 million people) had abused pain medication, 0.7 % tranquilizers (mostly benzodiazepines), 0.4 % stimulants (ADHD medication), and 0.1 % sedatives in 2008 (SAMHSA 2009).

38.4.1.2 Patient Surveys

The Drug Abuse Warning Network (DAWN) has gathered information on drugs mentioned at emergency room visits across the United States since 1974 and serves as a source of information about the extent of prescription drug abuse and gives signals on new drugs of abuse (Cai et al. 2010). The 2010 figures show that 30 % of the mentions on prescription drugs are benzodiazepines and 40 % are opioids. The drugs were mentioned in 20 % and 18 % of all emergency room visits, respectively, and prescription drugs were mentioned almost as often as narcotics. It is also of value getting information from patients entering treatment for drug abuse (Jaffe et al. 2004).

38.4.1.3 Adverse Effects Databases

Signals of prescription drug abuse often come from national or international adverse effects databases, such as the WHO in Uppsala Monitoring Centre Adverse

Effects Database. Such databases have given us information on the abuse liability of drugs like pregabalin (Gahr et al. 2013).

38.4.1.4 Forensic Data

Data from driving under the influence (DUI) cases, from autopsies, or from prisons may be useful in determining whether drugs are abused and which drugs are popular in which areas.

38.4.2 Monitoring Sources of Drugs

38.4.2.1 Sales Statistics

In the 1990s doctors started treating nonmalignant pain with opioids, and a sharp increase in the abuse of the drug has followed. As seen above in the total consumption model, the sales of the drugs can tell us something about the amount of problematic use (and other adverse events; see Fig. 38.1). The large sales of opioids in the United States are closely related to high levels of abuse. For example, among 12th graders in the United States, nonmedical use of prescription drugs (opioids) is the second most common form of abuse (Manchikanti et al. 2012). Sales data should be followed by area and/or country, because it gives useful hints on specific abuse trends.

38.4.2.2 Prescription Data

Prescription data are another source of information. These data stem from claims databases in insurance institutions; national prescription databases, such as those

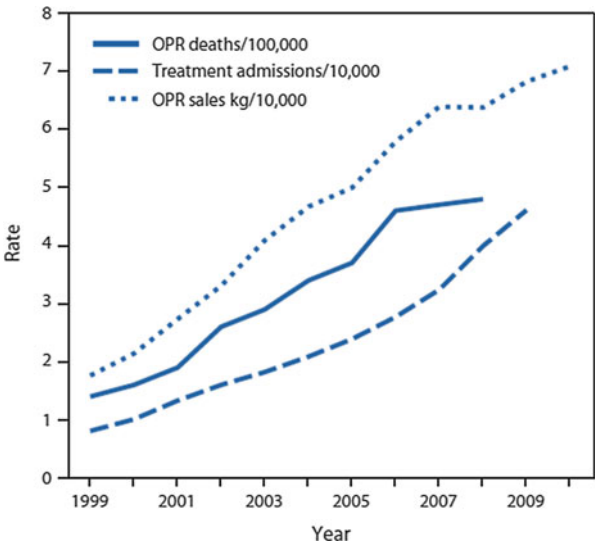

Fig. 38.1 Data on Rates* of opioid pain reliever (OPR) overdose death, OPR treatment admissions, and kilograms of OPR sold in United States (1999–2010). Data from US Centers for Disease Control and Prevention 2011

found in many countries in northern Europe; or through pharmacy records. Basically two types of information, both important, can stem from these sources. Firstly, we can gain information about the abuse liability of a drug by looking at phenomena like:

- "Doctor shopping": The more doctors a drug seeker is willing to go to in order to get hold of the drug, the higher the abuse liability (Peirce et al. 2012).
- Forged prescriptions: The more the prescriptions for a drug are forged, the higher the abuse potential (Frauger et al. 2012).
- High use of a drug: Indicating some using it for recreational purposes (Frauger et al. 2009; Pauly et al. 2011).
- Skewness in use: If a large part of the drug is consumed by a few individuals this is indicative of abuse liability (Gaist et al. 1997; Hallas and Støvring 2006).

Secondly, these sources of information might tell us directly how many individuals show overuse of the drugs in an area (Bramness et al. 2007). These data point to the fact that drugs like carisoprodol, clonazepam, flunitrazepam, alprazolam, and all opioids are attractive abuse drugs.

38.4.2.3 Other Legal/Gray Sources

Surveys in the normal population have shown that the most prevalent sources of prescription drugs for abuse are friends and family (McCabe 2008). This US study showed how pain medication was most often obtained; it may be different in other countries. Having a drug problem, using a lot of alcohol or having peers with use increased the risk. Still we know that many individuals start to abuse through drugs prescribed to a family member (Ballantyne 2007).

38.4.2.4 Illegal Sources

Prescription drugs, be it opioids, benzodiazepines, or others, are found on the black market. They are diverted illegally from people who have them prescribed, do not use them, but sell them. They are sold after thefts from patients, pharmacies or factories. Thus drug abuse situations can be monitored by looking at seizures of drugs by the police or customs.

38.4.2.5 Novel Channels of Drugs

The Internet is a novel source of drugs and very difficult to control. Only a small share of the drugs bought are ever discovered by customs. But turning it the other way around, monitoring the Internet can be a way of picking up new trends. One such project is the European Union funded Psychonaut Web Mapping Project that has been successful in identifying ever-increasing numbers of novel substances (Deluca et al. 2012). But data can also be collected by looking at websites for information or online reports of abuse (Schifano et al. 2011).

38.4.2.6 Wastewater Analysis

A novel approach that might give results in the future is to look at the presence of prescription drugs in wastewater (sewage analysis) (Reid et al. 2011). By comparing sales statistics with findings in wastewater, one could get an idea of the black

market for a drug, but also looking at weekly temporal variations in drugs, one might get a feeling how much is used for recreational use (most at weekends and less during weekdays) and how much is used on a regular basis (more evenly distributed).

Where does all this leave us? Firstly, we cannot today seriously say we know the extent of the problem of prescription drug abuse. No single source of data can substantiate all drugs that are abused or the extent of this abuse. Some data (surveys) will be flawed by information and selection bias; some data (databases) will not be able to identify the clinical features of abuse or dependence. We are therefore stuck with a number of estimates. And what do these tell us?

- These drugs are often used, but most use is clinically correct and well founded.
- Prescription drugs are, however, often abused and the problem of abuse is increasing.
- The size of the problem is related to total sales of the drug; increased use always comes at the price of increased abuse. Countries with a high prescribing rate (such as the United States) have a substantial problem. In such countries the problems following prescription drug abuse may equal those following the use of narcotic drugs.
- Some drugs have a higher abuse potential than others. As with other drugs of abuse, prescription drugs with high potency and a rapid effect will be more attractive to abusers.
- Patients who have legitimate use of these drugs are also at risk for abuse, and even use according to the doctor's recommendations can be problematic. Doctors should review their patient lists and take action when necessary.
- Specific populations will have more risk of abuse of prescription drugs than others. These include drug abusers, psychiatric patients, but also patients with somatic problems such as pain.
- It often takes a long time from when a drug is first marketed until its true abuse potential is revealed, even with modern requirements for pre-marketing investigations. Always be open to signals of a drug's abuse potential.

38.5 Strategies for Prevention

Having drugs available only on prescription is in itself a measure to control their use. The process of prescribing has come into place to increase the doctor's ability to monitor effects and adverse events, including abuse. Drugs with no or mild adverse effects may be sold without a prescription, so-called over-the-counter (OTC). However, even for these drugs, there may be regulations in place, such as age limitations on who is allowed to buy them, package size, and where the drugs may be placed for sale (are they on view to the customers?).

Other measures have been introduced to send signals on the abuse liability of medicinal drugs. How this is done will vary between countries, but basically there are two ways. First, it may include having rules and regulations on specific drugs

Table 38.6 Prescription drug are according to US health authorities classified after their potential for harm, including abuse. Not all drugs in this list are prescription drugs, but some are

Schedule	Definition	Most central drugs included
I	Drugs with no currently accepted medical use in treatment in the United States and high potential for abuse and dependence	Cathinone, GHB, heroin, LSD, marijuana, MDMA, most hallucinogens, methaqualone (Quaalude)
II	Drugs with currently accepted medical use in treatment with severe restrictions in the United States and high potential for abuse and dependence	Cocaine, amphetamines, other opiates than heroin, some opioids, some synthetic cannabinoids, barbiturates
III	Drugs with currently accepted medical use in treatment in the United States and with a lower risk for abuse than drugs in schedules I and II and low to moderate dependence risk	Anabolic steroids, some barbiturates, buprenorphine, codeine, ketamine, GHB as Xyrem, some synthetic cannabinoids
IV	Drugs with an accepted medical use in treatment in the United States and with a low risk for abuse and dependence (lower than III)	Benzodiazepines, benzodiazepine-like z-hypnotics, some barbiturates, carisoprodol
V	Drugs with a current accepted medical use in treatment in the United States and with a low risk for abuse and dependence (lower than IV)	Codeine, pregabalin, lacosamide, atropine

within the prescribing system, under the laws of medicinal drugs. This could imply different rules and regulations for prescribing these drugs compared to other drugs:

- The use of special prescribing.
- Only one doctor can prescribe to one patient.
- Only one pharmacy can deliver the drug.
- Only a specialist in a certain field can prescribe the drug.
- Special forms should be used for prescribing certain drugs.
- Special authorities should be informed and can perform controls/audits.
- Only certain package sizes can be prescribed.
- No telephone or Internet prescribing allowed for certain drugs.

Second, it could involve placing some medicinal drugs on narcotics lists and lists of controlled or prohibited substances. This places the drug under jurisdiction outside the health-care system and makes it police business. In many countries' legislative systems, these boundaries are not so clear and (often for historical reasons) illegal drugs and medicinal drugs are regulated by the same laws. The scheduling system in the United States is such a system (Table 38.6). The different degrees of scheduling can be followed by different rules or regulations for prescribing as mentioned in examples above.

One could imagine that having a regime of prescribing and scheduling would prevent widespread aberrant use, but this is not true. Aberrant use, be it abuse, dependence, or over-consumption, is seen despite these precautions. Research has shown us that the occurrence of overuse follows the sales of the drug in the

community or group and the prevalence of abuse can be predicted by sales, following the total consumption model. This model states that there is a close relationship between the population mean of a health variable, in this case prescribing of drugs with an abuse potential, and the prevalence of individuals at high risk concerning this variable (Skog 1980). The model applies for alcohol consumption and heavy drinkers and for the availability of narcotics drugs and has now been shown to apply for prescriptions drugs (Bramness and Rossow 2010). This understanding is important for two reasons. Firstly, a lot about aberrant drug use in a group or a country can be learnt from sales statistics. We do not always need clinical investigations! And secondly, preventive measures can be any procedure that will limit the prescribing of a drug. Such measures must always be weighed against what is good treatment. But this also teaches us that guidelines which open for liberal practices may have this downside.

We know that some doctors, independently of the profile of their patients, prescribe more drugs with abuse potential than others. This can be due to local traditions, to countrywide regulations, but also has to do with the doctor's own beliefs and ideas. Doctors with a liberal view on these drugs tend to prescribe more. This is also reflected in the doctors' own use of these drugs; doctors more willing to use these drugs themselves are also more willing to prescribe them to their patients (Rosvold et al. 1998).

Prescription drugs are to be sold after a consultation, after a review of the patient's problems, and by prescriptions. We see, however, an increasing sale of prescription drugs via the Internet. The police and customs face an almost impossible task trying to stop the import and illegal sales of prescription drugs via this route. Patients who get their drugs from the Internet pharmacies and the Internet pharmacies themselves are operating in a gray zone. We do not know the extent of this Internet market, but different estimates usually suggest enormous figures. There is a thin line between these sources and a true black market. The only way to deal with this is to appeal to people's reasoning and warn against the dangers of receiving a suboptimal product. Some of the products are of good quality, but others contain little or no active ingredient or even toxic material.

38.6 Treatment

The boundary between prevention and treatment is often obvious, but sometimes it can be unclear. Some preventive measures will be embedded in treatment and some experiences and views from treatment will be reflected in prevention.

38.6.1 Tackling the Drug-Seeking Patient

What kind of drug-seeking behavior physicians will encounter may vary according to their field but also according to their place or country of work. Some common

features can, however, be mentioned. Beware of lost prescriptions, lost medicines, or other reasons patients give for needing a prescription earlier (Isaacson 2000; Gerhardt 2004). Also be cautious prescribing drugs with abuse potential to patients you do not know. Optimally only one doctor should write drugs with an abuse potential to one patient, and these drugs should be given out only by one pharmacy. But if other doctors need to write prescriptions to patients that they do not know, they need to do a proper work-up and confirm diagnosis. The drugs with less abuse potential should be prescribed in the smallest possible quanta. Remember that you do not have to prescribe a whole package, even of the smallest package. The crux is to give your patients appropriate care. Withholding effective medication to needy patients is not an optimal alternative. Some institutions have policies for not prescribing drugs with an abuse potential to patients at certain times or under certain conditions. These institutions can report that they avoid a lot of drug-seeking patients, because word often spreads quickly if you cannot get what you want, but the institutions also risk not providing adequate treatment in some cases.

38.6.2 Minimal Interventions

If you, as a prescriber, are worried about a patient's use of prescription drugs, the first step is to discuss this with your patient. Open communication is of the essence. Even if the patient does not admit to a problematic relationship with these drugs, just verbalizing the issue may give them food for thought. Some doctors regularly review their patient lists and try to get a grip on who they should be concerned about. One strategy would be to send a letter of concern to the patients in question, just informing them of the potentially problematic sides to their drug use. Such a simple intervention has proven very efficient in stopping or reducing drug use in some patients (Mugunthan et al. 2011). Further support may be needed ("stepped care") and follow-up could include information meetings (pharmacology education), psycho-educative programs (information about the underlying disease and alternatives to pharmacological treatments), support groups, or even group therapy (Voshaar et al. 2006).

38.6.3 Tapering in the More Difficult Cases

Most studies show that gradual tapering of the medication is preferable to abrupt discontinuation (Parr et al. 2009; Denis et al. 2006). The use of anticonvulsants like carbamazepine or valproate can be of use for benzodiazepine withdrawal and clonidine for opioid withdrawal. Also some authors suggest the use of benzodiazepines for withdrawal from opioids, even if this can mean substituting one addiction with another (Fatseas and Auriacombe 2007). The main principle is to substitute short-acting drugs with longer-acting drugs, in order to have more control over the withdrawal symptoms.

38.6.4 Tapering the Patients with Benzodiazepine Dependence

A thorough evaluation must be performed of the actual dose the patient has been using. One should aim at reducing all the different benzodiazepines and benzodiazepine-like drugs to two different drugs at the most. Most often the recommendation is to switch to a longer-acting drug like diazepam (in most people) or a drug with fewer reinforcing effects like oxazepam (in drug abusers or the elderly). Remember that some benzodiazepines (e.g., alprazolam, clonazepam, and flunitrazepam) are 10–20 times more potent and need to be converted to equivalent diazepam doses. For good cooperation between you and your patient, you need to assure the patient that he/she will be adequately covered. For outpatient treatment you may want to taper by reducing 20 % of the total daily dose during the first months, then 10 % of the dose later, and then 5 % or less for the last weeks. Allow the patient to reach a steady state between dose reductions and allow for time to tackle the withdrawal symptoms. For adults with a half-life of 1–1.5 days of diazepam, one step can be performed every second week, but for older people the terminal elimination half-life of diazepam increases and more time should be allowed for each step. A lot of support and encouragement may be needed, sometimes in support groups, sometimes individually. For inpatient treatment a more aggressive approach is recommended. Often the patient will not be given enough time for a slow taper. The amount of withdrawal the patient needs to manage is constant either with short- or long-term tapering. Thus, in the inpatient situation a tapering of the whole dose within 2–3 weeks is recommended. You must then be aware of benzodiazepine delirium.

38.6.5 Tapering/Detoxifying the Patients with Opioid Dependency

The tapering of prescription opioids should always be done after a thorough work-up on pain and consideration of adequate pain management. For this we refer to textbooks on pain management. Even if inadequate pain management is the cause of the patient's problem, reduction or removal of the drugs will be needed. This would involve tapering. Such tapering can be more manageable using a long-acting opioid such as methadone or buprenorphine as a tool, even supported by clonidine to tackle the worst withdrawal symptoms. For further information on ▶ Chap. 28, "Opioid Addiction: Short- and Long-Acting Opioids".

38.6.6 Intoxications

Acute treatment of intoxications with prescription drugs should be handled as other emergencies. Life support including airways, breath, and circulation should be observed. Gastric lavage can be performed if necessary and when done within a limited amount of time. For opioids and benzodiazepines, there are antidotes in naloxone and flumazenil. Otherwise drugs should be given on indication.

Benzodiazepine delirium: This should be treated like an alcoholic delirium tremens. Reinstating benzodiazepines and tapering them at a slower pace would be the preferred mode.

38.7 International Perspectives

There are huge differences in the availability of psychotropic drugs worldwide. While Europe and North America constitute 12 % and 7 % of the world's population, respectively, these continents consume 83 % of the world's prescription opioids (1996–2000 data) (Ghodse 2003); this figure is over 90 % when we look at ADHD drugs. The good news is that many countries outside Europe and North America have fewer problems with prescription drug abuse. This gives these countries the possibility of choosing another way, with fewer problems concerning these drugs. We must however remember that this may render some patients undertreated for their maladies.

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Further Reading

There are several books on recovery stories by patients who have quit the habit of benzodiazepines or opioids. These can be illustrative and helpful for other people trying to stop taking these drugs. One problem may be a lack of perspective in these stories of prescription-drug abuse survivors. They often lack perspective on what drugs are harmful and what drugs are not and on the fact that some people need these drugs for their treatment, while others are better off not using them. Two books that can be recommended are:

- Hobson-Dupont J (2006) The Benzo book: getting safely off tranquilizers. Essex Press. A personal story with good advice on benzodiazepine withdrawal
- Johns B (2010) Benzo-wise: a recovery companion. Campanile Publishing. A personal story with good advice on benzodiazepine withdrawal

One piece of further reading that is not out in book form, but is readily available on the internet is The Ashton Manual:

- Ashton H. Benzodiazepines: how they work and how to withdraw. http://www.benzo.org.uk/manual/. This holds information about benzodiazepines and sets up schemes for tapering. The web page (supported by Roche!) has many hints and supports for people coming off prescription drugs

Regulatory Aspects of New Medications to Treat Addictions: The U.S. IND Process

39

Robert L. Walsh

Contents

Abstract

In most countries, for a medication to be available to treat addictions, it must first go through a development and approval process. In the United States, the Center of Drug Evaluation and Research (CDER), of the Food and Drug Administration (FDA), is the Federal agency responsible for approving new addiction pharmacotherapies based upon their safety and efficacy. The Investigational New Drug (IND) application is the means by which FDA allows a new medication to be studied in humans. In order to be able to test a potential medication for addiction in humans, FDA requires certain tests to be conducted to (1) characterize the

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chemical properties of the molecule so that it can be manufactured and formulated reliably over several batches, (2) determine the toxicological properties of the medication so that it can be administered at safe doses, (3) ensure that anticipated toxicities can be monitored for in a study to avoid irreparable harm to study subjects, and (4) identify potential interactions that may occur when the medication is used in combination with the drug of abuse. This chapter will provide an overview of the IND process, the sections of an application, maintenance of an IND, and important meetings and identify the conditions for which a study is exempt from requiring an IND.

39.1 Regulatory Aspects

39.1.1 The Investigational New Drug (IND) Process

Current US Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. The Federal Food, Drug, and Cosmetic Act (FD&C Act), section 355 – New drugs states that "No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) of this section is effective with respect to such drug." Because a sponsor often manufactures the drug in one location and then needs to ship the investigational drug to clinical investigators in many states and/or countries, it has to seek an exemption from that legal requirement. The IND is the mechanism through which the sponsor technically obtains this exemption from the FDA.

In the United States, the sponsor of an IND must have a US address or agent. The US Code of Federal Regulations, 21 CFR 312.23 (a)(1)(ix), states that a sponsor shall include in the IND application "The signature of the sponsor or the sponsor's authorized representative. If the person signing the application does not reside or have a place of business within the United States, the IND is required to contain the name and address of, and be countersigned by, an attorney, agent, or other authorized official who resides or maintains a place of business within the United States." Often sponsors outside of the United States, who do not maintain offices in the United States, will use a contract research organization (CRO) to act as their agent for the IND.

Before studies in humans can begin, an Investigational New Drug (IND) application must be submitted to the FDA containing, among other things, information on any risks anticipated based on the results of pharmacological and toxicological data collected during studies of the drug in animals as outlined in 21 CFR 312.23(a)(8). These basic safety tests are often performed in mice, rats, and dogs. The studies are designed to allow a sponsor to identify a safe starting dose to give the drug to humans. The studies also allow a sponsor to gain an understanding of which organs may be the targets of toxicity, to estimate the margin of safety between a clinical and a toxic dose, and to predict pharmacokinetic and pharmacodynamic parameters. The central focus of the initial IND submission should be on the general investigational plan and the protocols for specific human studies.

An IND enables a sponsor to communicate all of the known information about a potential medication to FDA for the agency to review. FDA's primary objectives in reviewing an IND are to assure that the safety and rights of subjects are protected and to assure that the quality of the scientific evaluation is adequate to permit an evaluation of the drug's effectiveness and safety.

Upon receipt of an IND, the FDA has 30 days to make a determination as to whether the proposed study in humans may proceed. Generally, in about 1–2 weeks after submitting the IND, the sponsor will receive a letter of receipt showing the date the IND was received at FDA. This date is when the 30-day review clock is measured from.

If no feedback is provided by FDA, verbally or in writing, the study may proceed as submitted after the 30 days has passed. This is an important point because, in these cases, a sponsor often does not receive a letter stating that the study may proceed.

When approximately 15 days have passed after receipt of the IND, the internal FDA review team may meet and discuss any concerns they may have regarding their review of the IND. If there are concerns, they will contact the sponsor and try to resolve the concerns before the 30-day clock runs out in order to avoid placing the IND on "clinical hold," as required under 21 CFR 312.42. If the safety concerns cannot be resolved within the 30-day time frame, FDA will contact the sponsor (usually in a teleconference) and inform them that the IND is being put on "clinical hold." If an IND is placed on clinical hold, no studies in humans may proceed until all of the safety concerns are addressed to FDA's satisfaction. FDA will provide a "clinical hold letter," within 30 days from the date of the teleconference, which describes in detail the reasons for the IND being placed on clinical hold. Upon receipt of that letter, the sponsor must respond, in writing, to the FDA detailing how they will address the concerns identified by FDA.

When the sponsor has addressed all of the clinical hold issues identified in the letter, it will have provided a "complete response." FDA will then respond to the sponsor within 30 days of receipt of the complete response indicating whether the hold is lifted, or if not, specifying the reasons why not. After an IND is placed on clinical hold, studies may not be initiated in humans until FDA contacts the sponsor (via phone, fax, letter, or e-mail) informing them that the study may proceed.

The IND is used to update FDA on the progress throughout the development life cycle of a potential medication to the submission of a marketing application known as a New Drug Application (NDA). The IND is also the mechanism which allows the sponsor to obtain input regarding protocol design, report adverse events, and provide final study reports and results to the FDA.

39.1.2 The Investigational New Drug (IND) Application

The amount of information, on a particular drug, that must be submitted in an IND can vary greatly and will depend upon such factors as the novelty of the drug, the extent to which it has been studied previously, the known or suspected risks, and the developmental phase of the drug.

The IND application is comprised of multiple sections which are differentiated into:

1. Cover Sheet
2. Table of Contents
3. Introductory Statement and General Investigational Plan
4. Investigator's Brochure
5. Protocol(s) (Clinical)
6. Chemistry, Manufacturing, and Control Information
7. Pharmacology/Toxicology Information
8. Previous Human Experience
9. Additional Information

39.1.2.1 The Cover Sheet

The cover sheet introduces the IND application to the FDA. It identifies who the sponsor is and to whom correspondence should be communicated to.

39.1.2.2 Table of Contents

The table of contents identifies the sections and subsections of the IND and on what pages they can be found.

39.1.2.3 Introductory Statement and General Investigational Plan

The introductory statement and general investigational plan section(s) is intended to be only about 2–3 pages in length. The information presented here is to put the sponsor's development plan for the drug into perspective and to help FDA anticipate the sponsor's future needs, such as when critical meetings might need to take place. This helps the agency to identify potential "crunch times" when a number of critical items may need to be addressed in the same time period.

This section provides the name of the drug and all active ingredients, the drug's pharmacological class, the structural formula of the drug (if known), the formulation of the dosage form(s) to be used, the route of administration, and the broad objectives and planned duration of the proposed clinical investigation(s).

39.1.2.4 The Investigator's Brochure (IB)

The investigator's brochure is a compilation of all of the clinical and nonclinical data known on the potential medication which is relevant to the study of the product in human subjects. The purpose of the IB is to provide the investigators, and others involved in the trial, with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration, and safety monitoring procedures. The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial.

The IB typically contains:

- A brief description of the drug substance and the formulation, including the structural formula, if known
- A summary of the pharmacological and toxicological effects of the drug in animals and, to the extent known, in humans
- A summary of the pharmacokinetic and biological disposition of the drug in animals and, if known, in humans
- A summary of information relating to safety and effectiveness in humans obtained from prior clinical studies (reprints of published articles on such studies may be appended when useful)
- A description of possible risks and side effects to be anticipated on the basis of prior experience with the drug under investigation or with related drugs and of precautions or special monitoring to be done as part of the investigational use of the drug

Often the information needed for the IB can be obtained from the summary that is included at the front of each of the IND sections. This document can also be valuable to Institutional Review Board/Institutional Ethics Committee members to help with their review of the proposed study and to help them determine the potential risks to subjects.

39.1.2.5 Protocol

The protocol section of the IND contains a protocol for each planned study. It is expected that protocols for phase 1 studies may be less detailed and more flexible than protocols for phases 2 and 3 studies. Phase 1 protocols should be directed primarily at providing an outline of the investigation – an estimate of the number of patients to be involved, a description of safety exclusions, and a description of the dosing plan including duration, dose, or method to be used in determining dose – and should specify in detail only those elements of the study that are critical to safety, such as necessary monitoring of vital signs and blood chemistries. For phase 1 studies of potential medications for drug addiction, it is important to also include what measures (i.e., medications and medical equipment that will be available at all times during the study, training and availability of staff, etc.) will be taken to anticipate for any unexpected life-threatening events that may occur during the conduct of the study.

For phase 1 studies of potential medications for drug addiction, it is important to also detail what measures (i.e., medications and medical equipment that will be available at all times during the study, availability of appropriately trained medical staff, etc.) will be taken to anticipate any unexpected life-threatening events such as cardiac arrest or another serious adverse event that may occur during the conduct of the study. The measures proposed need to be well thought out and should give an FDA reviewer a sufficient level of comfort that unexpected serious adverse events have been anticipated and planned for.

In phases 2 and 3, detailed protocols describing all aspects of the study should be submitted. A protocol for a phase 2 or 3 investigation should be designed in such a way that if the sponsor anticipates that some deviation from the study design may

become necessary as the investigation progresses, alternatives, or contingencies to provide for such deviation are built into the protocols at the outset. For example, a protocol for a controlled short-term study might include a plan for an early crossover of nonresponders to an alternative therapy.

Phase 2 studies should be designed to identify measurable outcome measures that could be used in the phase 3 studies to definitively prove the efficacy of the medication. Often a phase 2 study will have one primary, and multiple secondary, outcome measures. They can then be analyzed to determine which one may be the best choice as the primary outcome measure to be used in a pivotal phase 3 study.

39.1.3 Chemistry, Manufacturing, and Controls (CMC)

The regulations at 21 CFR 312.23 (a)(7)(i) emphasize the graded nature of chemistry, manufacturing, and controls (CMC) information needed as development under an IND progresses. Although in each phase of a clinical investigational program, sufficient information should be submitted to ensure the proper identification, strength, quality, purity, and potency of the investigational candidate, the amount of information needed which will provide that assurance will vary with the phase of the investigation, the proposed duration of the investigation, the dosage form, and the amount of information already available.

The emphasis in an initial phase 1 CMC submission should be placed on providing information, detailing the identification and control of the raw materials and the new drug substance. This will allow an evaluation of the safety of subjects in the proposed study.

This section should contain a brief description of the overall plan for investigating the drug product for the following year. Detailed developmental plans are often contingent on the outcome of the planned study(ies). In that case, sponsors should simply state this and not try to develop overly detailed plans.

The plan should include the following:

(a) The rationale for the drug or the research study
(b) The indication(s) to be studied
(c) The general approach to be followed in evaluating the drug
(d) The kinds of clinical trials to be conducted in the first year following the submission (if plans are not developed for the entire year, the sponsor should so indicate)
(e) The estimated number of patients to be given the drug in those studies
(f) Any risks of particular severity or seriousness anticipated on the basis of the toxicological data in animals or prior studies in humans with the drug or related drugs

39.1.4 Pharmacology/Toxicology

The development of a medication is a stepwise process involving an evaluation of both animal and human safety information. The goals of the nonclinical safety

evaluation include characterizing the toxic effects of the potential medication with respect to:

- Target organs
- Dose dependence
- Relationship to exposure
- Potential reversibility

This information is important to estimate an initial safe starting dose for the human trials and to identify parameters to allow clinical monitoring for potential adverse effects. The nonclinical safety studies, which may be limited at the beginning of clinical development, should be adequate to characterize any potential toxic effects which may be anticipated under the conditions of the proposed clinical trial.

The pharmacology/toxicology section should contain adequate information about the pharmacological and toxicological studies of the drug involving laboratory animals or in vitro, which the sponsor used as the basis for concluding that it is reasonably safe to evaluate the potential medication in human subjects.

The kind, duration, and scope of animal and other tests required vary with the duration and nature of the proposed clinical investigation. Such information is required to include the identification and qualifications of the individuals who evaluated the results of such studies and concluded that it is reasonably safe to begin the proposed investigations and include a statement of where the investigations were conducted and where the records may be made available for inspection.

The nonclinical safety study recommendations for the marketing approval of a pharmaceutical usually include single and repeated dose toxicity studies, reproduction toxicity studies, genotoxicity studies, local tolerance studies, and, for drugs that have special cause for concern or are intended for a long duration of use, an assessment of carcinogenic potential. Other nonclinical studies include pharmacological studies for safety assessment (safety pharmacology) and pharmacokinetic (absorption, distribution, metabolism, and excretion (ADME)) studies.

An additional aspect of developing medications to treat addiction is the need for animal drug-drug interactions studies with drugs of abuse. Since drug users often abuse multiple drugs, it is necessary to know not only whether the potential medication will interact with the specific drug of abuse it is being developed for but also whether it will interact with other commonly co-abused drugs. To address that concern the potential medication is tested against cocaine, morphine, and alcohol in animals prior to initiating phase 2 studies. These studies serve to alert the sponsor and FDA of any particular interaction that could occur in humans.

The types of studies that are summarized in the pharmacology/toxicology section of the initial IND application are those that were conducted to support initial and early clinical development studies.

39.1.5 Previous Human Experience

If the investigational drug has been investigated or marketed previously, detailed information relevant to the safety of the proposed investigation or to the

investigation's rationale should be provided. If the drug has been studied in controlled clinical trials, detailed information on those trials, relevant to an assessment of the drug's effectiveness for the proposed investigational use(s), should be included. If there is no known human experience with the investigational drug that should be stated in this section.

Copies of any published material relevant to the safety of the proposed investigation or to an assessment of the drug's effectiveness for its proposed investigational use should be provided in full. Published material that is less directly relevant can be included in a bibliography.

If the drug is a combination of drugs previously investigated or marketed, information should be provided for each active drug component. However, if any component in such combination is subject to an approved marketing application or is otherwise lawfully marketed in the United States, the sponsor is not required to submit published material concerning that active drug component unless such material relates directly to the proposed investigational use (including publications relevant to component-component interaction).

If the drug has been marketed outside the United States, a list of the countries in which the drug has been marketed and a list of the countries in which the drug has been withdrawn from marketing and the reason for the withdrawal must be included.

39.1.6 Additional Information

In certain applications, information on special topics may be needed. The types of information to be submitted in this section are:

1. Drug dependence and abuse potential – If the drug is a psychotropic substance or otherwise has abuse potential, information describing what relevant studies have been done is identified here. Information from both human and animal studies should be included.
2. Radioactive drugs – If the drug is a radioactive drug, sufficient data from animal or human studies to allow a reasonable calculation of radiation-absorbed dose to the whole body and critical organs upon administration to a human subject should be provided. Phase I studies of radioactive drugs must include studies which will obtain sufficient data for dosimetry calculations.
3. Pediatric studies – Proposed plan for assessing pediatric safety and effectiveness should be provided.
4. Other information – A brief statement of any other information that might aid the evaluation of the proposed clinical investigations with respect to their safety or their design. The ability of the studies to be considered as controlled, clinical trials to support marketing of the drug should also be discussed.

39.1.7 IND Meetings

39.1.7.1 Pre-IND Meeting

Prior to the submission of the initial IND, the sponsor can request a meeting with FDA-reviewing officials. The primary purpose of this meeting is to review and

reach agreement on the adequacy of the chemical information and animal studies needed to initiate human testing. The meeting may also provide an opportunity for discussing the scope and design of phase 1 testing, plans for studying the drug product in pediatric populations, and the best approach for presentation and formatting of data in the IND.

CDER's Pre-Investigational New Drug Application (IND) Consultation Program fosters early communications between sponsors and new drug review divisions to provide guidance on the data necessary to warrant IND submission. The review divisions are organized generally along therapeutic class and can each be contacted using the designated Pre-IND Consultation List (Fig. 39.1).

39.1.7.2 End of Phase 2 Meeting

The end of phase 2 meeting is often considered to be the most critical meeting held during an investigational drug's development process. The main objectives of an end of phase 2 meeting are:

- To obtain agreement with FDA on pivotal study designs and safety and efficacy endpoints for phase 3 studies. This is to ensure that the planned pivotal studies will provide the information and data required to obtain approval for marketing the medication in the United States.
- To update the agency as to the progress of pharmacokinetic (PK) studies and to discuss additional studies that may be needed. This will ensure that any issues raised as a result of the PK studies and/or other safety concerns that may exist for a specific population are addressed.
- To agree that the preclinical data with regard to duration, route of administration, and formulation are supportive of the dose to be used in the phase 3 clinical trials.
- To discuss the intended approach to specifications and test methods to ensure that the methods to be used to manufacture the medication are appropriate and will provide the necessary information regarding impurities and batch-to-batch consistency.
- To discuss the intended "marketed" formulation.
- To identify other issues or potential problems (novel regulatory or technical concerns).

39.1.8 Drug Master File Program

A Drug Master File (DMF) is submitted to the FDA to provide confidential, detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs. This can be valuable in cases where a sponsor is opening multiple INDs on the same investigational drug (such as for different indications) since the sponsor can provide a letter of authorization to allow FDA staff to cross-reference the information on behalf of the IND applicant rather than having to provide the identical information in each IND application. It is also useful when a sponsor wishes to support the

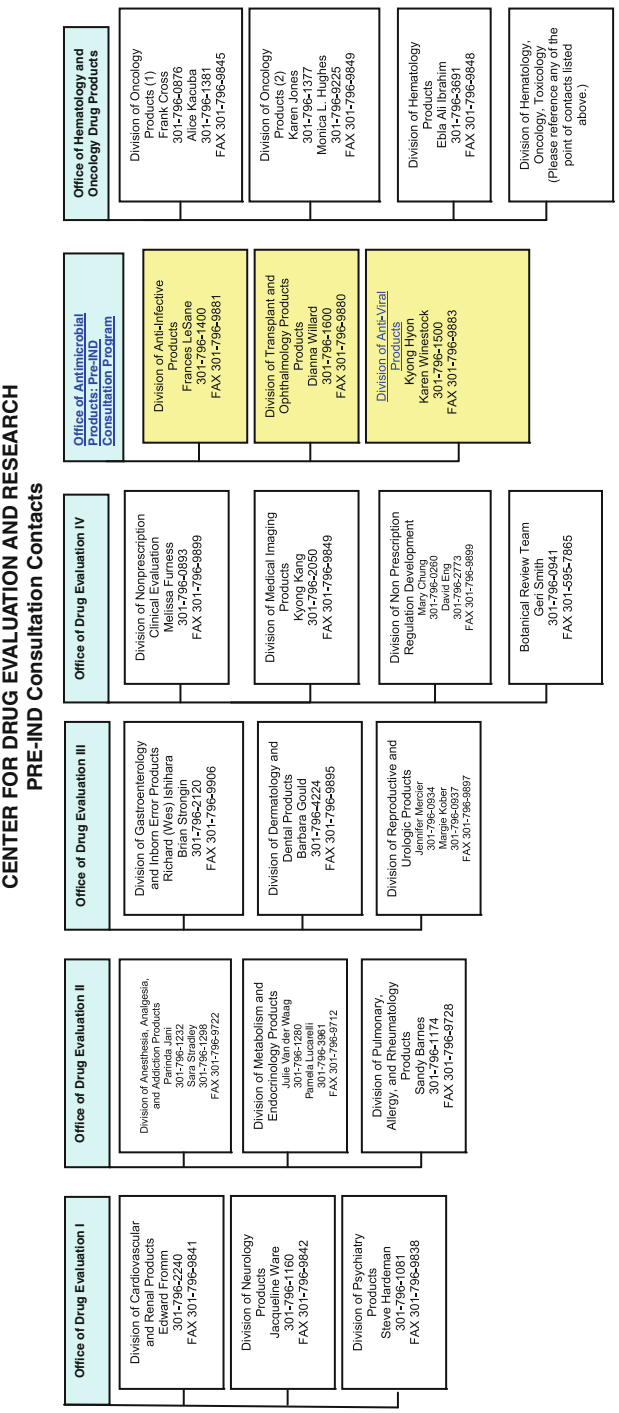

Fig. 39.1 CDER pre-IND consultation contacts

submission of an IND by other investigators but does not wish to provide confidential chemical information about the investigational drug.

A DMF is not required by law or FDA regulation. A DMF is submitted solely at the discretion of the holder. The information contained in the DMF may be used to support an Investigational New Drug Application (IND), a New Drug Application (NDA), an Abbreviated New Drug Application (ANDA), another DMF, an Export Application, or amendments and supplements to any of these.

A DMF is NOT a substitute for an IND, NDA, ANDA, or Export Application. It is not approved or disapproved. Technical contents of a DMF are reviewed only in connection with the review of an IND, NDA, ANDA, or an Export Application.

As stated in 21 CFR 10.90(b), this guideline does not impose mandatory requirements. It does, however, offer guidance on acceptable approaches to meeting regulatory requirements. Different approaches may be followed, but the applicant is encouraged to discuss significant variations in advance with FDA reviewers to preclude spending time and effort in preparing a submission that FDA may later determine to be unacceptable.

Drug Master Files are provided for in 21 CFR 314.420. The guideline is intended to provide DMF holders with procedures acceptable to the agency for preparing and submitting a DMF. The guideline discusses types of DMFs, the information needed in each type, the format of submissions to a DMF, the administrative procedures governing review of DMFs, and the obligations of the DMF holder.

DMFs are generally created to allow a party other than the holder of the DMF to reference material without disclosing to that party the contents of the file. When an applicant references its own material, the applicant should reference the information contained in its own IND, NDA, or ANDA directly rather than establishing a new DMF.

There are five types of DMFs:

- Type I: Manufacturing Site, Facilities, Operating Procedures, and Personnel
- Type II: Drug Substance, Drug Substance Intermediate, and Material Used in Their Preparation, or Drug Product
- Type III: Packaging Material
- Type IV: Excipient, Colorant, Flavor, Essence, or Material Used in Their Preparation
- Type V: FDA Accepted Reference Information

Each DMF should contain only one type of information and all supporting data. See Section IV.C of the guideline for more detailed descriptions of the kind of information desired in each type. Supporting information and data in a DMF can also be cross-referenced to any other DMF.

39.1.9 Letters of Authorization to FDA

Before FDA can review DMF information in support of an application, the DMF holder must submit, in duplicate to the DMF, a letter of authorization permitting FDA to reference the DMF. If the holder cross-references its own DMF, the holder

should supply in a letter of authorization the information designated by items 3, 5, 6, 7, and 8 of this section. The holder does not need to send a transmittal letter with its letter of authorization.

The letter of authorization should include the following:

- The date
- Name of DMF holder
- DMF number
- Name of person(s) authorized to incorporate information in the DMF by reference
- Specific product(s) covered by the DMF
- Submission date(s) of 5 above
- Section numbers and/or page numbers to be referenced
- Statement of commitment that the DMF is current and that the DMF holder will comply with the statements made in it
- Signature of authorizing official
- Typed name and title of official authorizing reference to the DMF

The DMF holder should also send a copy of the letter of authorization to the requesting applicant, sponsor, or other holder who is authorized to incorporate by reference the specific information contained in the DMF. The applicant, sponsor, or other holder referencing a DMF is required to include a copy of the DMF holder's letter of authorization in their IND application.

It is important to remember that "A DMF IS NEVER APPROVED OR DISAPPROVED."

The FDA only reviews the information in a DMF when an IND sponsor; an applicant for an NDA, ANDA, or Export Application; or another DMF holder incorporates material in the DMF by reference in their application. As noted, the incorporation by reference must be accompanied by a copy of the DMF holder's letter of authorization. This verifies that FDA may use the information contained in the DMF on behalf of the party that is referencing it in their application.

If FDA reviewers find deficiencies in the information provided in a DMF, a letter describing the deficiencies is sent to the DMF holder. At the same time, FDA will notify the person who relies on the information in the deficient DMF that additional information is needed in the supporting DMF. The general subject of the deficiency is identified, but details of the deficiency are disclosed only to the DMF holder. When the holder submits the requested information to the DMF in response to the agency's deficiency letter, the holder should also send a copy of the accompanying transmittal letter to the requesting persons relying on the DMF and to the FDA-reviewing division that identified the deficiencies. The transmittal letter will provide notice that the deficiencies have been addressed.

39.1.10 Exemption from IND

A drug that is lawfully marketed in the United States is exempt from the requirements for an IND if ***all*** of the following apply:

1. The investigation is not intended to be reported to the FDA in support of a new indication for use or any other significant change in the labeling for the drug.
2. The investigation is not intended to support a significant change in the advertising for a prescription drug product.
3. The investigation does not involve a change in route of administration, dosage level, patient population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with use of the drug product.
4. The investigation is conducted in compliance with the requirements for IRB review (21 CFR 56) and informed consent (21 CFR 50).
5. The drug may not be represented as safe or effective for the purposes for which it is under investigation nor may it be commercially distributed or sold.

It is important to note that *all* of the criteria above must be met in order to qualify for an exemption. Often the marketed medication being studied for a different indication is being used at a different dosage level or in a different patient population than that which it was originally studied in. These conditions would require an IND to be obtained.

The FDA Draft Guidance Investigational New Drug Applications (INDs) – Determining Whether Human Research Studies Can Be Conducted Without an IND provides more detail on a range of issues, including the process for consulting with FDA if unsure.

39.1.11 Guidance Documents for INDs

Guidance documents represent the agency's current thinking on a particular subject. These documents provide FDA review staff and applicants/sponsors with guidelines to the processing, content, and evaluation/approval of applications and also to the design, production, manufacturing, and testing of regulated products. They also establish policies intended to achieve consistency in the agency's regulatory approach and establish inspection and enforcement procedures.

Because guidances are not regulations or laws, they are not enforceable, either through administrative actions or through the courts. An alternative approach may be used if it satisfies the requirements of the applicable statute, regulations, or both. For a complete list of CDER guidances, please go to CDER's Guidance Index on the FDA website.

Some specific guidance documents that are helpful when preparing INDs include:

39.1.11.1 Maintaining an IND

To maintain an IND, the sponsor-investigator has three reporting responsibilities. Each type of report is time-sensitive and has a specific structure. The first two, protocol amendments and safety reports, are submitted when needed to report updated or unforeseen circumstances. The third type, the annual report, is submitted every year, even when no studies are in progress under the IND. The IND sponsor must send all submissions to the address provided in the IND acknowledgment letter received from FDA in response to the initial submission.

39.1.11.2 IND Protocol Amendments

Once an IND is in effect, the IND sponsor-investigator is responsible to amend it as needed to ensure that the clinical investigations are conducted according to protocols included in the application. An IND protocol amendment is a submission to an existing IND which notifies the FDA of one or more of the following:

- A new study protocol
- A change in an existing study protocol
- A new investigator

39.1.11.3 IND Safety Reports

An IND safety report is expedited, written notification to the FDA of an adverse experience associated with the use of a study drug that is both serious and unexpected. "Associated with the use of the drug" is a *Code of Federal Regulations* term meaning, "There is a reasonable possibility that the experience may have been caused by the drug." An IND safety report consists of a MedWatch form and a cover letter. It is due to the FDA within 15 calendar days of initial receipt of the SAE report.

39.1.11.4 IND Annual Reports

An IND annual report is a brief report of the progress of studies conducted under an IND, due annually to the FDA within 60 days of the anniversary of the date that the IND went into effect.

39.1.12 Fast Track, Accelerated Approval, Breakthrough Therapies, and Priority Review

Speeding the development and availability of drugs that treat serious diseases are in everyone's interest, especially when the drugs are the first available treatment or have distinct advantages over existing treatments. The Food and Drug Administration (FDA) has developed four distinct and successful approaches to making such drugs available as rapidly as possible: priority review, accelerated approval, breakthrough therapies, and fast track. Because each of these approaches implies speed, there can be confusion about the specific meaning of each and the distinctions among them.

39.1.12.1 Fast Track

Fast track is a process designed to facilitate the development and expedite the review of drugs to treat serious diseases and fill an unmet medical need. The purpose is to get important new drugs to the patient earlier. *Fast track* addresses a broad range of serious diseases.

Determining whether a disease is *serious* is a matter of judgment but generally is based on whether the drug will have an impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one. AIDS, Alzheimer's, heart failure, and cancer are obvious examples of serious diseases. However, diseases such as epilepsy, depression, and diabetes are also considered to be serious diseases.

Filling an *unmet medical need* is defined as providing a therapy where none exists or providing a therapy which may be potentially superior to existing therapy.

Any drug being developed to treat or prevent a disease with no current therapy obviously is directed at an unmet need. If there are existing therapies, a fast track drug must show some advantage over available treatment, such as:

- Showing superior effectiveness
- Avoiding serious side effects of an available treatment
- Improving the diagnosis of a serious disease where early diagnosis results in an improved outcome
- Decreasing a clinically significant toxicity of an accepted treatment
- A drug that receives *fast track* designation is eligible for some or all of the following:
- More frequent meetings with FDA to discuss the drug's development plan and ensure collection of appropriate data needed to support drug approval
- More frequent written correspondence from FDA about such things as the design of the proposed clinical trials
- Eligibility for *accelerated approval*, i.e., approval on an effect on a surrogate or substitute endpoint reasonably likely to predict clinical benefit
- *Rolling review*, which means that a drug company can submit completed sections of its New Drug Application (NDA) for review by FDA, rather than waiting until every section of the application is completed before the entire application can be reviewed. NDA review usually does not begin until the drug company has submitted the entire application to the FDA.
- Dispute resolution if the drug company is not satisfied with an FDA decision not to grant fast track status.

In addition, most drugs that are eligible for fast track designation are likely to be considered appropriate to receive a *priority review*. *Fast track* designation must be requested by the drug company and can be initiated at any time during the drug development process. FDA will review the request and make a decision within 60 days based on whether the drug fills an unmet medical need in a serious disease.

Once a drug receives *fast track* designation, early and frequent communication between the FDA and a drug company is encouraged throughout the entire drug development and review process. The frequency of communication assures that questions and issues are resolved quickly, often leading to earlier drug approval and access by patients.

39.1.12.2 Accelerated Approval

When studying a new drug, it can take a long time – sometimes many years – to learn whether a drug actually provides real improvement for patients, such as living longer or feeling better. This real improvement is known as a "clinical outcome." Mindful of the fact that obtaining data on clinical outcomes can take a long time, in 1992 FDA instituted the *accelerated approval* regulation, allowing earlier approval of drugs to treat serious diseases and that fill an unmet medical need based on a surrogate endpoint.

A surrogate endpoint is a marker – a laboratory measurement or physical sign – that is used in clinical trials as an indirect or substitute measurement that

represents a clinically meaningful outcome, such as survival or symptom improvement. The use of a surrogate endpoint can considerably shorten the time required prior to receiving FDA approval.

Approval of a drug based on such endpoints is given on the condition that post marketing clinical trials verify the anticipated clinical benefit.

The FDA bases its decision on whether to accept the proposed surrogate endpoint on the scientific support for that endpoint. The studies that demonstrate the effect of the drug on the surrogate endpoint must be "adequate and well controlled," the only basis under law for finding that a drug is effective.

Use of a surrogate can save valuable time in the drug approval process. For example, instead of having to wait to learn if a drug actually can extend the survival of cancer patients, the FDA might now approve a drug based on evidence that the drug shrinks tumors because tumor shrinkage is considered *reasonably likely to predict* a real clinical benefit. In this example, an approval based upon tumor shrinkage can occur far sooner than waiting to learn whether patients actually lived longer. The drug company will still need to conduct studies to confirm that tumor shrinkage actually does predict that patients will live longer. These studies are known as phase 4 confirmatory trials.

If the confirmatory trial shows that the drug actually provides a clinical benefit, then the FDA grants traditional approval for the drug. If the confirmatory trial does not show that the drug provides clinical benefit for patients, FDA has regulatory procedures in place that could lead to removing the drug from the market.

39.1.12.3 Priority Review

Prior to approval, each drug marketed in the United States must go through a detailed FDA review process. In 1992, under the Prescription Drug User Act (PDUFA), FDA agreed to specific goals for improving the drug review time and created a two-tiered system of review times – standard review *and* priority review.

Standard review is applied to a drug that offers at most only minor improvement over existing marketed therapies. The 2002 amendments to PDUFA set a goal that a standard review of a new drug application be accomplished within a 10-month time frame.

A priority review designation is given to drugs that offer major advances in treatment or provide a treatment where no adequate therapy exists. A priority review means that the time it takes FDA to review a new drug application is reduced. The FDA goal for completing a priority review is 6 months.

Priority review status can apply both to drugs that are used to treat serious diseases and to drugs for less serious illnesses.

The distinction between priority and standard review times is that additional FDA attention and resources will be directed to drugs that have the potential to provide significant advances in treatment.

Such advances can be demonstrated by, for example:

- Evidence of increased effectiveness in treatment, prevention, or diagnosis of disease
- Elimination or substantial reduction of a treatment-limiting drug reaction
- Documented enhancement of patient willingness or ability to take the drug according to the required schedule and dose
- Evidence of safety and effectiveness in a new subpopulation, such as children

A request for *priority review* must be made by the drug company. It does not affect the length of the clinical trial period. FDA determines within 45 days of the drug company's request whether a *priority* or *standard review* designation will be assigned. Designation of a drug as "priority" does not alter the scientific/medical standard for approval or the quality of evidence necessary.

Fast track, accelerated approval, breakthrough therapies, *and* priority review are approaches that are intended to make therapeutically important drugs available at an earlier time. They do not compromise the standards for the safety and effectiveness of the drugs that become available through this process.

These revitalized FDA drug review approaches have yielded tangible results in bringing safe and effective drugs to patients with serious diseases more quickly. For example, since 1996, 68 drugs for cancer therapies have received priority review and approval.

FDA reviewed Gleevec, a treatment for chronic myeloid leukemia, in 4 months. Shortened review times have also brought promising treatments to patients with HIV/AIDS more quickly. Kaletra for the treatment of HIV/AIDS was reviewed and approved in 3.5 months. Pegasys, a combination product for the treatment of Hepatitis C, was approved for marketing in 4 months.

Fast track, accelerated approval, breakthrough therapies, *and* priority review have evolved over time. FDA has been vigilant in assuring that reducing the time necessary for drug development has not compromised the safety and effectiveness of drugs for patients with serious diseases.

39.2 Conclusion

Hopefully this chapter has been helpful in describing the contents of an IND and the IND process for drug development in general but with particular emphasis on pharmacotherapies for substance use disorders. It should be remembered that this is a high-level overview and there is much more detail that needs to be considered when submitting an IND application. A knowledgeable US regulatory affairs expert can greatly improve the odds that an IND application is acceptable to FDA. A successful IND requires great attention to detail and clear presentation of the information provided. It is also important to try and anticipate the regulator's questions and provide complete answers to those questions in the application, thereby greatly reducing the chance for a clinical hold being imposed.

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Biologics (Vaccines, Antibodies, Enzymes) to Treat Drug Addictions

40

Ivan D. Montoya

Contents

Abstract

A novel approach for the treatment of substance use disorders (SUDs) is the use of biologics. Biologics include immunotherapies, such as vaccines or antibodies, as well as enzymes. These are usually large and complex molecules that do not cross the blood-brain barrier and do not have effects in the central nervous system (CNS). Biologics are investigated for the treatment of SUDs because they prevent the access of the drug of abuse to the brain and, thus, prevent their effect of brain reward systems. It is expected that over a period of treatment with biologics, they will help to produce an extinction of the brain mechanisms of drug dependence. SUDs are complex medical conditions that require multiple therapeutic approaches and the treatment with biologics may offer a new way to treat these disorders without directly affecting the brain. The purpose of this chapter is to provide a general overview of the current status of research with vaccines, antibodies, and enzymes for the treatment of SUDs.

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40.1 Introduction

Substance use disorders (SUDs) are complex clinical conditions with multiple medical and psychosocial manifestations. SUDs require multiple treatment approaches, including the use of psychosocial interventions and often pharmacotherapies. Over the past 20 years, significant strides have been made in the understanding, development, and availability of medications to treat SUDs. Medications such as methadone, buprenorphine, and naltrexone (oral and injectable long-acting formulations) for opiate use disorders as well as nicotine replacement therapy, bupropion and varenicline for nicotine dependence, have shown to be safe and effective interventions for the respective disorders.

There is a great need for new approaches to treat SUDs because the long-term efficacy of the approved medications to maintain drug use abstinence is far from ideal. Also, the fact that there are no medications approved by regulatory agencies for the treatment of cocaine, methamphetamine, and cannabis use disorders makes this need even more urgent (Montoya and Vocci 2008). Traditionally, the development of pharmacotherapies for SUDs has focused on small molecule approaches that target a receptor or neurotransmitter in the brain. An alternative approach is the use of biologics.

The Food and Drug Administration (FDA) of the United States defines biological products as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings" (US Food and Drug Administration 1999). Biologics are generally "large" molecules derived from living material, complex in structure, usually not fully characterized, which do not cross the blood-brain barrier and have no CNS effects. Biologics can be extracted from living systems (e.g., extracted from tissues), originated from stem cells, produced by recombinant DNA, produced in bioreactors, or engineered in a laboratory.

The concept of using biologics to treat SUDs was first described in 1974 in a study conducted in monkeys that received morphine immunization and showed a reduction in heroin self-administration (Bonese et al. 1974). Subsequently, new biologics have been discovered and tested with the goal of treating treat nicotine, cocaine, methamphetamine, opiates, and phencyclidine use disorders (Kinsey et al. 2009; Zheng and Zhan 2009).

It has been suggested that the mechanism of action of biologics to treat SUDs is by preventing the access of the drug of abuse to the brain. This, in turn, prevents the activation of brain reward systems by the drug. The long-term effect of biologics is expected to produce a behavioral extinction of the addictive behavior. Also, by preventing the access of the drug of abuse to the brain, biologics may help to treat drug overdose (Peterson and Owens 2009). The biologics currently investigated include vaccines, antibodies, and enzymes.

Vaccines stimulate the immune system to recognize the drug of abuse as a foreign substance (antigen) and produce antibodies to combat it. Given that

drugs of abuse are small molecules with low ability to stimulate the immune response, they can become immunogenic by conjugating them on to a foreign carrier protein. The immune system of vaccinated individuals forms an antigen (the drug of abuse)–antibody complex in plasma. This complex is a large molecule that does not cross the blood-brain barrier and prevents the access of the drug of abuse to the brain (Peterson and Owens 2009; Anton et al. 2009; Gentry et al. 2010; Orson et al. 2008). Animal studies have been conducted with vaccines against nicotine, cocaine, amphetamine, and heroin. Human studies have been conducted with vaccines against nicotine and cocaine.

Antibodies are being investigated to treat SUDs as well as drug overdose. Antibodies bind directly in plasma to the drug of abuse and prevent it from reaching the brain almost immediately after the administration. Therefore, they have the advantage of not needing the immune system to block the access of the drugs of abuse to the brain. This effect makes them ideal candidates for the treatment of the neuropsychiatric complications of drug overdose. Antibodies are being investigated for the treatment of cocaine dependence as well as cocaine, methamphetamine, and phencyclidine overdose (Zheng and Zhan 2009; Carroll et al. 2011; Gentry et al. 2010).

Engineered enzymes significantly more efficient than wild enzymes are being investigated for the treatment of SUD and overdose. These enzymes can rapidly metabolize the drug of abuse before it reaches the brain. They may be more effective than antibodies or vaccines when the drug concentration in plasma is high, as is the case of an overdose. They can also be treatment tools and as such a recombinant long-acting mutated butyrylcholinesterase that is being investigated for cocaine dependence (Gao et al. 2010; Brimijoin et al. 2008; Zheng et al. 2008; Godin et al. 2012).

Presently, new and improved products and technologies offer vast opportunities to advance the discovery and development of biologics to treat SUDs. Some of these advancements include the discovery and development of nontraditional vaccines and adjuvants, new monoclonal antibodies, and means of extending their biological half-life, as well as highly efficient engineered enzymes that can metabolize a drug of abuse orders of magnitude faster than the wild enzyme. The purpose of this chapter is to provide an overview of the current research with vaccines, antibodies, and enzymes for the treatment of nicotine, cocaine, opiates, and methamphetamine use disorders.

40.2 Biologics Applications

40.2.1 Nicotine Dependence

Several vaccines have been investigated with the goal of treating nicotine dependence. They include NicVax™ (produced by Nabi Biopharmaceuticals), NIC002 (Nicotine Qbeta therapeutic vaccine, Cytos Biotechnology), SEL-068 (Selecta Biosciences using a proprietary Synthetic Vaccine Particle [SVP™]),

PF-05402536 (Pfizer), TA-NIC vaccine (Celtic Pharma), and IP18-KLH (Niccine, investigators at the Karolinska Institute in Sweden and Independent Pharmaceutica).

NicVax is the anti-nicotine vaccine that has reached the most advanced phase of therapeutic development. This vaccine has good immunogenicity and appears to be safe and effective, particularly among individuals who produced high antibody titers. A randomized, double-blinded, placebo-controlled multicenter clinical trial, in a sample of 301 smokers, evaluated NicVAX at doses of 200 and 400 μg; four or five times over a period of 6 months showed that subjects with the highest serum anti-nicotine antibody response were significantly more likely to achieve 8 weeks of continuous abstinence from weeks 19 through 26 than those who received placebo injection (Hatsukami et al. 2011). Unfortunately, two phase III clinical trials with a total sample of approximately 2,000 subjects failed to demonstrate the primary endpoint, which was nicotine abstinence rate (defined by self-reported cigarette use and exhaled carbon monoxide measures) for 16 weeks ending at 12 months of treatment. It appears that efforts to continue the development of this vaccine have been abandoned (Nabi Pharmaceuticals 2012).

NIC002 uses as the carrier protein viruslike particles covalently coupled with nicotine. A placebo-controlled, clinical trial with NIC002 at a dose of 100 μg showed that this vaccine had good immunogenecity, was well tolerated, and showed efficacy in a subgroup of subjects who achieved high antibody levels after vaccination. These results were considered a clinical proof of concept (Cytos Biotechnology 2012). A phase II clinical trial ($n = 65$) evaluated the pharmacokinetics/pharmacodynamics of nicotine during cigarette smoking in individuals treated with four subcutaneous injections of 100 μg of NIC002 at 4-week intervals (Cytos Biotechnology 2012). The results did not support the study's primary endpoint and on January, 2013 Cytos announced Novartis will discontinue the smoking cessation project with NIC002.

SEL-068 is a new vaccine approach that uses nanotechnology methods. It consists of synthetic immunomodulatory nanoparticles that home to antigen-presenting cells (dendritic cells and B cells) to produce highly efficient antigen-specific immune responses. This targeted Synthetic Vaccine Particles (tSVP™) can activate immune responses to relevant antigens such as nicotine. A phase I double-blind, placebo-controlled clinical trial was initiated with the goal of assessing the concentrations of nicotine-specific antibodies in response to different doses of the vaccine, as well as the safety and possible efficacy for smoking cessation and relapse prevention (Selecta Biosciences 2012).

PF-05402536 is currently in phase I studies for exploration and optimization with the goal of inducing high-avidity antibodies to block effectively nicotine in the blood of smokers. The company claims that in preclinical models this vaccine has reached antibody of avidity and strength that go far beyond what has been studied before in this area (Pfizer 2012; McCluskie et al. 2013).

TA-NIC vaccine uses the cholera toxin-B subunit as a carrier protein (Celtic Pharma 2012). Results from a multicenter, double-blind, randomized, placebo-controlled, clinical trial showed that the vaccine was not better than placebo.

The company attributes this failure to problems with the manufacturing of the vaccine (Celtic Pharma 2012).

IP18-KLH (Niccine) is an anti-nicotine vaccine developed by investigators in Sweden. It is an immunoconjugate IP18-KLH that prevents the access of nicotine to the brain and does not precipitate nicotine withdrawal in rats (de Villiers et al. 2002, 2010). A randomized, double-blind study in a sample of 355 smokers showed that this vaccine was well tolerated but was not able to induce the production of sufficient antibodies against nicotine. Therefore, it was considered not efficacious for smoking relapse prevention (Tonstad et al. 2013).

40.2.2 Cocaine Dependence

Several groups of investigators are working in developing anti-cocaine vaccines such as TA-CD, dAd5GNC, and GNC92H2 (Fox et al. 1996; Hicks et al. 2011; Kantak 2003; Kosten et al. 2002; Martell et al. 2005), monoclonal antibodies, and enzymes to treat cocaine dependence.

TA-CD vaccine is being developed by Celtic Pharma. It uses succinylnorcocaine coupled to a nontoxic subunit of recombinant cholera toxin B with aluminum hydroxide as the adjuvant. A phase IIb clinical trial was conducted in a sample of 114 cocaine-dependent outpatients receiving treatment with methadone. A secondary analysis showed that subjects with the highest IgG antibody titers ($\geq$43 μg/ml) had a significantly greater proportion of cocaine-free urine samples. Recently, a multi-site, double-blind, randomized clinical trial conducted in a sample of 300 cocaine-dependent subjects was completed and the results did not support the efficacy of this vaccine to treat cocaine dependence (results unpublished) (www.clinicaltrials.gov NCT00969878) (Martell et al. 2005; Kosten et al. 2002; Kinsey et al. 2010).

TV-1380 is a human plasma butyrylcholinesterase (BChE) that is being developed by Teva Pharmaceuticals Ltd. It is a fusion of a mutant BChE enzyme with human serum albumin. It has extended catalytic activity, prolonged plasma half-life, and good stability. BChE metabolizes cocaine into ecgonine methyl ester and benzoic acid, which have little toxicity and lack rewarding actions (Brimijoin et al. 2008; Zheng et al. 2008). Studies suggest that TV-1380 has no adverse cardiovascular and respiratory reactions and appears to attenuate the cardiovascular effects produced by cocaine in monkeys (Godin et al. 2012). Phase II studies to determine the safety and efficacy of TV-1380 for the treatment of cocaine dependence are being planned. RBP-8000 is a highly efficient bacterial cocaine esterase (CocE). It is a long-acting mutant form of a naturally occurring bacterial esterase. In pre-clinical studies, this esterase has been able to antagonize the convulsing, reinforcing, discriminative, cardiovascular and lethal effects of cocaine (Collins et al. 2012). A study conducted in rats showed that whey they were treated with RBP-8000 and exposed to high doses of cocaine they improved survival, food consumption, body weight and liver function tests as compared to those that were not treated with the enzyme. The authors suggest that RBP-8000 has a "rescue"

effect for cocaine toxicity (McGee and Godin 2013). Currently, a randomized, double-blind study is evaluating pharmacokinetics parameters of RBP-8000 and cocaine to determine the effects of RBP-8000 on cocaine-induced physiologic and behavioral effects (http://clinicaltrials.gov/ct2/show/NCT01846481).

dAd5GNC is an anti-cocaine vaccine that consists of linking the capsid protein of an adenovirus to the cocaine molecule. The administration of dAd5GNC to mice elicits a production of antibodies that is capable of preventing the access of cocaine to the brain. Also, this vaccine is capable of reversing the hyperlocomotor activity produced by the administration of cocaine. Therefore, it may be useful to treat of cocaine dependence as well as cocaine overdose (Hicks et al. 2011).

GNC92H2 is an immunoglobuline G (IgG) with extended half-life that may sequester cocaine in blood and prevent its access to the brain. It appears that this vaccine has the capacity to redistribute cocaine from the brain to serum, within the restricted timeframe of cocaine overdose. Further research needs to be conducted to determine the medical safety and therapeutic utility of GNC92H2 for cocaine overdose (Treweek et al. 2011).

40.2.3 Methamphetamine Dependence

Immunotherapeutic approaches to methamphetamine and amphetamine dependence and overdose also appear promising (Gentry et al. 2009, 2010; Moreno et al. 2011; Duryee et al. 2009; Carroll et al. 2009). Gentry et al. reported that anti-methamphetamine monoclonal antibodies (mAb) are able to antagonize the locomotor effects of methamphetamine in rats and decrease meth-induced elevations in blood pressure and heart rate. Therefore, anti-methamphetamine mAb may prevent neurotoxicity and cardiovascular complications associated with methamphetamine overdose (Gentry et al. 2009). Recently, investigators began clinical trials of this mAb for the treatment of methamphetamine dependence.

EP54 is a methamphetamine vaccine that has been able to generate serum antibody titers against methamphetamine (Duryee et al. 2009). Efforts to systematic generate a series of haptens designed to target methamphetamine are ongoing. Vaccination of mice with meth immunoconjugates has shown high antibody titers and high affinity for three particularly promising formulations (Moreno et al. 2011).

40.2.4 Opiate Dependence

The development of biologics to treat opiate dependence is particularly challenging. The potentially efficacious vaccine should be able to bind to its target(s) with high specificity and avoid interfering with both the endogenous and any prescribed opiate medication. The ideal anti-opiate vaccine is one that can produce antibodies against heroin or the target opiate without blocking the pharmacotherapeutic effects of other opiates.

Currently, several groups are investigating anti-opiate vaccines (Anton and Leff 2006; Anton et al. 2009; Li et al. 2011; Pravetoni et al. 2012; Stowe et al. 2011). M-TT is being developed by a group of investigators in Mexico (Anton and Leff 2006; Anton et al. 2009). It has been reported that it is a highly immunogenic bivalent morphine/heroin vaccine that uses the tetanus toxoid as protein carrier. Studies conducted in rats have shown that the vaccine was able to prevent opiate use relapse.

M-KLH is a morphine (M) and oxycodone (OXY) haptens conjugated vaccine that may be useful for the treatment of poly-opioid dependence. A recently published study conducted in rats showed that M-KLH alone produced high titers of antibodies directed against heroin, 6-monoacetylmorphine (6-MAM), and morphine. Future studies are needed to determine the efficacy of bivalent anti-opioid vaccines that may simultaneously target multiple abusable opioids (Pravetoni et al. 2013).

40.3 Conclusion

Given the public health burden of the SUDs and overdose, there is an urgent need for safe and effective therapeutic interventions and biologics appear to be a promising approach. Development process include the anti-nicotine vaccine PF-05402536. With regard to biologics against cocaine, TA-CD and TV-1380 are the most advanced. Biologics to treat opiate and methamphetamine dependence are far behind.

As with any other psychiatric condition, the biologic treatments must be provided in conjunction with adequate psychosocial support. The ideal biologic-based therapy should be potent enough to block the access of the drug of abuse to the brain for a long period of time and should have good specificity for the target drug or class of drugs. The long-acting effect is important because individuals with SUDs usually have poor treatment adherence and extended effects will increase the probability of successful outcomes.

Biologics have the advantage of exerting their effect in the periphery. Unlike pharmacotherapies that work by altering brain functions, biologics do not cross the blood-brain barrier and therefore are unlikely to produce undesirable neuropsychiatric side effects. If necessary, biologics can be combined with pharmacotherapies which may result in boosting their therapeutic effect. Given that vaccines rely on the immune system for the production of antibodies, it is required that the immune system of the host will have capability of producing the antibodies.

Biologics are large molecules that may have unique metabolic characteristics and could cause a whole sort of possible adverse events such as kidney or liver problems. Also, because they are usually originated from living organisms, there is always a risk of anaphylactic complications. One of the drawbacks of vaccines is that they may be contraindicated in people with SUDs who have immunodeficiencies, poor nutrition, or chronic and debilitating medical conditions. The medical safety is an important issue in the development of treatments with biologics.

Currently, there is a great need of safe and effective biologics to treat SUDs. Research is needed to develop vaccines that can elicit high levels of antibody titers

and adjuvants that can improve their immunogenicity, as well as technologies to improve the specificity and efficiency of production of vaccines. Given the accelerated pace of this area of research, it is expected that in the near future there will be safe and effective biologics that health-care providers can use to treat their patients with SUDs.

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Recent Advances in Drug Development

41

Frank J. Vocci

Contents

Abstract

Encouraging findings are being reported in the development of drugs for the treatment of addictive disorders. This chapter reviews drug development for the treatment of alcohol, cannabis, cocaine, opiates, and methamphetamine dependence. Gabapentin, pregabalin, ondansetron, and sertraline have been investigated for the management of alcohol dependence in double-blind, placebo-controlled designs. Gabapentin has been shown in two studies to reduce the emergence and percentage of heavy drinking days following alcohol detoxification treatment. Pregabalin was shown to reduce withdrawal

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symptomatology, craving, and relapse. Sertraline was reported to be efficacious in reducing drinking days and heavy drinking days in study participants with late-onset alcoholism. Ondansetron was shown to reduce drinks per drinking day and to increase the percentage of days abstinent in an alcohol-dependent population. Gabapentin has been shown to reduce cannabis use, withdrawal, and craving relative to a placebo group in one study. Nabilone has been shown to reduce marijuana withdrawal symptoms and self-administration in a clinical laboratory study, providing a rationale for an outpatient trial. A combination of mixed amphetamine salts and topiramate, compared to a placebo group, produced a greater percentage of cocaine-dependent participants achieving 3 weeks of continuous abstinence. Bupropion, methylphenidate, naltrexone, and topiramate have been evaluated for efficacy in facilitating abstinence in methamphetamine dependence. Bupropion has given the strongest signals of efficacy. Topiramate may have some utility as a relapse prevention agent but this needs to be confirmed.

Implantable and injectable forms of buprenorphine are being developed for the treatment of opioid dependence.

41.1 Introduction

The development of medications for the treatment of addictive disorders has had some successes in the treatment of alcohol dependence (acamprosate, oral and extended-release naltrexone, and disulfiram), nicotine dependence (nicotine replacement therapies and bupropion), and opioid dependence (methadone, oral and extended-release naltrexone, buprenorphine, and buprenorphine/naloxone), while there are no marketed pharmacotherapies for the treatment of cannabis, cocaine, or methamphetamine dependence. There are 26 medications in development for addictive disorders by the pharmaceutical industry (Pharmaceutical Research Manufacturers Association [PhRMA] report 2012). Some of these development projects are partially supported by funding from the US National Institutes of Health. Of these 26 medications, some are being investigated for multiple drug dependencies. Thus, there are seven medications being evaluated for each of cocaine, opiate, and nicotine dependencies, while there are five medications being developed for alcohol dependence treatment and three for methamphetamine dependence treatment. Additionally, the medications development programs of the National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism support clinical studies of investigational and marketed medications that are not on the list from the PhRMA. Reviewing all the medications on the PhRMA list is beyond the scope of this chapter. This review will survey developments for the treatment of alcohol, cannabis, cocaine, opiates, and methamphetamine dependence that were recently published in the medical literature.

41.2 Medications in Development for Treatment of Substance Use Disorders

41.2.1 Pharmacological Treatments for Alcohol Dependence

Gabapentin (GPN) is an antiepileptic medication that is also indicated for the treatment of post-herpetic neuralgia in the United States. It has been studied as a treatment for the prevention of alcohol relapse. It is often used in the immediate post-detoxification period. The results of the four randomized, double-blind studies are summarized in Table 41.1. The daily dose of GPN ranged from 600 to 1,500 mg in these studies. GPN has a salutary effect on the reemergence of heavy drinking days, the percentage of heavy drinking days, and often had a posttreatment effect that lasted weeks (Brower et al. 2008) or months (Anton et al. 2009).

Pregabalin is another GABA analog that has been studied as a relapse prevention agent in alcohol-dependent populations. Three studies have been conducted by Martinotti's group and are summarized in Table 41.2. Doses of 150–450 mg per day were tested in an open-label design (Martinotti et al. 2008), a randomized single-blind comparison to lorazepam and tiagabine (Martinotti et al. 2010a), and a double-blind comparison to naltrexone (Martinotti et al. 2010b). The following scales were used in the studies: Clinical Institute Withdrawal Assessment of Alcohol Scale-Revised (CIWA-AR), the Symptom Checklist 90-Revised, and the Obsessive-Compulsive Drinking Scale (OCDS). The studies show a consistent reduction in withdrawal symptomatology, craving, and relapse, with a greater effect on relapse seen in patients with an Axis I diagnosis. The results suggest that pregabalin has promise in the prevention of relapse in alcoholic patients and may be indicated for alcoholic patients with co-occurring psychiatric disorders. However, since there is only one double-blind study, further confirmation of the efficacy of pregabalin is needed, preferably by other clinical sites.

Two studies examined the interaction of medications with a single-nucleotide polymorphism of the serotonin transporter gene (5′-HTTLPR) and age of onset of alcoholism in order to resolve previous inconsistencies reported for serotonergic medications on drinking behavior and alcoholism treatment (see Kranzler et al. 2011). Kranzler evaluated the effect of sertraline on 134 patients with a diagnosis of moderate to severe alcohol dependence. An urn randomization procedure was used to balance the sertraline and placebo-treated groups on the following variables: age of onset of alcoholism (early-onset alcoholism [EOA] or late-onset alcoholism [LOA]), current age, gender, educational level attained, past diagnosis of major depressive disorder, and duration of abstinence prior to screening). All study participants were genotyped for the tri-allelic 5′-HTTLPR single-nucleotide polymorphism (SNP), designated as SS/LS/LL. Participants were initially treated with 50 mg of sertraline or matching placebo and then the dose was increased to a maximum of 200 mg of sertraline. Medication was provided for 12 weeks and then tapered over a 2-week interval. The dependent variables of interest were drinking days (DDs) and heavy drinking days (HDDs).

Table 41.1 Clinical studies of the efficacy of GPN in the treatment of alcohol dependence

Study design	Sample size	GPN dose and duration	Comparator medication	Results	Reference
Randomized, double blind	60 males	300 mg bid for 30 days	Placebo	GPN reduced the number of drinks per day, % heavy drinking days both ($p = 0.02$) and increased % days abstinent ($p = 0.008$)	Furieri and Nakamura-Palacios (2007)
Randomized, double blind	11 males and 10 females	Titration up to 1,500 mg per day. Dosed for 6 weeks	Placebo	GPN reduced onset to heavy drinking effect relative to placebo; effect persisted for 6 weeks ($p = 0.003$ at 12 weeks)	Brower et al. (2008)
Randomized, double blind	60	Titration up to 1,200 mg; dosed for 39 days. 2 doses of flumazenil (2 mg) on 2 successive days	Placebo GPN and placebo flumazenil	GPN differential efficacy: better modulation of withdrawal in those with more severe withdrawal, more % days abstinent and more time to first heavy drinking episode. Effects persisted for 8 weeks post-dosing	Anton et al. (2009)
Randomized, double blind	150; 119 male	Titration up to 1,200 mg per day with or without 50 mg naltrexone per day	Respective placebos	First 6 weeks: GPN/naltrexone group had longer delay to heavy drinking ($p = 0.04$) and less heavy drinking days than naltrexone only group ($p = 0.0002$) and less drinks/drinking day than naltrexone only group ($p = 0.02$) and placebo group ($p = 0.01$)	Anton et al. (2011)

One hundred thirty-four participants were randomized: 63 to sertraline (21 EOAs and 42 LOAs) and 71 participants received placebo (25 EOAs and 46 LOAs). Completion rates varied across the groups, being the lowest in the LL EOAs treated at 14.3 % with sertraline and highest in the LL EOAs who received placebo and LL LOAs who received sertraline (83.3 % in both groups). There was no significant difference noted in participants that possessed the S allele. The results for DDs and HDDs varied by age of onset in the homozygous L carriers. LOAs receiving sertraline had fewer DDs and fewer HDDs ($p = 0.011$) compared to LOAs receiving placebo whereas the EOA group had fewer DDs and HDDs when

Table 41.2 Effects of pregabalin on relapse to drinking in alcoholic patients

Study design	Sample size	Pregabalin dose and duration	Comparator medication	Results	Reference
Open label	31 enrolled (16 males 15 females), 20 received drug	150–450 mg/day; $X = 262.5$ mg 16 weeks dosing	None	10 of 15 completers were abstinent for the trial duration; significant reductions in craving on OCDS and VAS (both $p < 0.001$); statistically significant decreases CIWA alcohol score, Symptom Checklist 90-R and subscales rating obsessive-compulsive, hostility/anger, and psychoticism, General Severity Index, and Positive Symptom Total	Martinotti et al. (2008)
Randomized, multicenter, single blind	190 evaluated, 111 enrolled 69 males 42 females, $N = 37$/group	Up to 450 mg per day for 2 weeks	Lorazepam up to 10 mg/day for 14 days; tiapride up to 800 mg/day for 14 days	All groups had significant withdrawal score reduction on the CIWA alcohol scale with a greater effect of pregabalin on headache and orientation ($p < 0.001$); all groups reported less craving; less relapse in the pregabalin group ($p < 0.05$); less retention in the tiapride group ($p < 0.05$)	Martinotti et al. (2010a)
Randomized, double blind	71 enrolled 54 males, 59 detoxed $N = 31$ pregabalin, $N = 28$ naltrexone Both groups have had equivalent Axis I comorbid patients	Up to 450 mg/day, $X = 275.8$ mg/day for 16 weeks; 27/31 completed	Naltrexone 50 mg/day; for 16 weeks; 21/28 completed	No group differences in abstinence or craving scores; % of abstinent pregabalin patients with dual diagnosis was significantly higher than in the naltrexone group ($p < 0.05$); CIWA-AR scores reduced in both groups, with a greater reduction in the pregabalin group ($p < 0.05$)	Martinotti et al. (2010b)

treated with placebo. A follow-up study at 3 and 6 months post-medication discontinuation noted that the sertraline effect on DDs and HDDs was still evident in the LOAs at 3 ($p = 0.027$) but not 6 months (Kranzler et al. 2012). These provocative findings support further studies with sertraline for the treatment of alcohol dependence. A confirmatory study should also include EOAs as a negative control group.

Johnson and colleagues (2011) evaluated the effects of a low dose (4 μg/kg) of ondansetron (OND), a 5HT 3 antagonist, versus placebo on drinks per drinking day (D/DDs) and the percentage of days abstinent (DAb). Study participants were genotyped for the tri-allelic 5′-HTTLPR SNP, designated as SS/LS/LL, as well as a second SNP (T/G) rs1042173 in the 3′-untranslated region of the 5-HTT gene. Genotyping for the RS1042173 SNP was performed after randomization. An urn randomization procedure was used in this trial to assign participants to OND or placebo with respect to the LL, LS, and SS genotypes. Two hundred eighty-three DSM-IV diagnosed alcohol-dependent participants were enrolled. They were mostly white males (73 % white, 84 % male) and the rest were Hispanic. A placebo run-in was used in the first week. Thereafter, OND or placebo was supplied for 11 weeks to the study participants.

OND recipients possessing the LL genotype had a greater, statistically significant therapeutic response in terms of both D/DD and % DAb with effect sizes in the medium range (Table 41.3). LL carriers with the additional TT genotype had an enhanced, statistically significant response to OND when compared to all other OND recipients, all placebo recipients, LL/TT carriers who received placebo, and LL/G carriers. Effect sizes for D/DD were in the large range and for % DAb were in the medium range.

It has been previously reported that individuals with the LL genotype have a greater urge to drink (Ait-Daoud et al. 2009). The enhanced efficacy of OND blockade of 5-HT3 receptors in this group suggests that the 5-HT3 system may be sensitized in these individuals.

41.2.2 Pharmacotherapy of Cannabis Dependence

There are no currently marketed pharmacotherapies for the treatment of cannabis dependence. Two research groups have evaluated medications marketed for other indications in cannabis-dependent populations. The first study evaluated gabapentin (GPN) in 50 cannabis-dependent adults (88 % male) in a randomized, double-blind, placebo-controlled design (Mason et al. 2012). GPN was administered at a dose of 1,200 mg per day for 12 weeks in an outpatient setting. Cannabis use was determined by assaying delta-9 tetrahydrocannabinol (THC) concentrations in weekly urine samples and by self-report using the timeline followback interview procedure. Cannabis withdrawal was quantified using the Marijuana Withdrawal Checklist. The consequences of cannabis use were determined by the Marijuana Problems Scale. The last 38 enrollees were further assessed on three sub-tests of the Delis-Kaplan Executive Function Test: trail-making, color-word interference, and the verbal fluency tests.

Table 41.3 Effects of genotype on the response to OND

Group	Comparison	D/DD mean difference	*P* value	Cohen's d	% Dab mean difference	*P* value	Cohen's d
OND	LL vs. LS/SS genotypes	−1.53	0.005	0.47	9.73	0.03	0.29
LL genotype	OND vs. placebo	−1.62	0.007	0.56	11.27	0.023	0.41
LL genotype	LS/SS OND + LL placebo + LS/SS placebo combined	−1.45	0.002	0.45	9.65	0.013	0.32
LL/TT OND	All other OND recipients	−2.57	0.0002	0.92	15.50	0.008	0.62
LL/TT OND	All placebo recipients	−2.67	0.0001	0.86	17.98	0.002	0.65
LL/TT OND	LL/TT placebo	−2.06	0.015	0.72	12.52	0.079	0.51
LL/TT	LL/G carriers	−2.34	0.005	0.82	15.25	0.03	0.62

Relative to the findings in the placebo group, GPN reduced cannabis use as determined by weekly urine toxicology ($p = 0.001$) and self-report results ($p = 0.004$). GPN also significantly reduced withdrawal symptoms ($p = 0.001$), craving ($p = 0.001$), and Beck Depression Inventory scores ($p = 0.009$). Sleep was also improved in the GPN group as determined by the Pittsburgh Sleep Quality Index ($p < 0.001$). The GPN medicated group showed improvement, relative to their baseline scores, on the Marijuana Problems Scale score ($p = 0.02$). The GPN group also showed greater improvement relative to placebo on a composite score of the three executive function tests ($p = 0.029$). GPN is a promising candidate medication for the treatment of cannabis dependence. The results need to be replicated before GPN can be recommended as a treatment for cannabis dependence.

Nabilone is a synthetic cannabinoid medication. It has been compared to THC (dronabinol) in a clinical pharmacology study of its subjective, cognitive, and cardiovascular effects in ten current adult marijuana smokers (Bedi et al. 2012). Nabilone (2 mg) decreased systolic blood pressure and higher doses (4, 6, 8 mg) produced cannabinoid-like subjective effects. Doses of 6 or 8 mg of nabilone decreased psychomotor speed. Nabilone had a slower time to peak effects than THC and its effects were more dose-related than THC. The authors speculated that the dose-relatedness might be due to nabilone having more reliable bioavailability that THC.

A second study evaluated nabilone's ability to affect marijuana withdrawal symptoms and a measure of relapse (Haney et al. 2013). Eleven marijuana smokers were administered three doses of nabilone (0, 6, and 8 mg) in a counterbalanced order during times of marijuana abstinence (three consecutive days of placebo marijuana) in the clinical pharmacology laboratory. Both active doses of nabilone decreased marijuana withdrawal-related irritability and sleep disruptions ($p < 0.05$).

Food intake was increased relative to placebo when 6 or 8 mg doses of nabilone were administered during the marijuana withdrawal period. Participants engaged in more eating sessions ($p < 0.01$) and increased the caloric intake during each eating session. Nabilone doses of 6 and 8 mg also reduced self-administration of marijuana puffs, a laboratory measure of marijuana relapse. Interestingly, nabilone did not produce "liking" or a desire to take the nabilone capsules.

The data from the two studies discussed above suggest that nabilone should be evaluated as a treatment for cannabis dependence. The clinical pharmacology studies provide a rationale and the dose range for a phase II outpatient study.

41.2.3 Pharmacotherapy of Cocaine and Amphetamine/Methamphetamine Dependence

A combination of extended-release mixed amphetamine salts and topiramate was evaluated for efficacy in the treatment of cocaine dependence by Mariani et al. (2012).

These investigators randomized 81 cocaine-dependent study participants to the combination of mixed amphetamine salts and topiramate or their respective placebos. The mixed amphetamine salts were titrated to a maximum dose of 60 mg daily over a 2-week period, while the topiramate was ramped up to a maximum dose of 150 mg bid over 6 weeks. The primary outcome was the proportion of participants per group that achieved 3 weeks of continuous abstinence during the 12-week trial period.

The mixed amphetamine salt and topiramate group had twice the number of participants achieving the 3-week abstinence criterion than the placebo group (33 % vs. 17 %, respectively). Moreover, the higher the baseline use of cocaine, the more effective the active treatment combination was ($p < 0.05$). The median time to onset of the first week of 3 weeks continuous abstinence was 5 weeks in the amphetamine/topiramate group and 3 weeks in the placebo group. The onset of abstinence in the amphetamine/topiramate group came near the end of the topiramate titration period. The positive signal from this initial trial suggests that the drug combination of extended-release mixed amphetamine salts and topiramate deserves further study.

Modafinil was reported to facilitate abstinence (3 weeks continuous abstinence criterion) in cocaine-dependent subjects in a randomized, double-blind, placebo-controlled trial (Dackis et al. 2005). Subsequently, two confirmatory studies were performed. The first was a double-blind, placebo-controlled, and multicenter trial evaluation of 200 and 400 mg doses of modafinil in 210 cocaine-dependent subjects with or without a history of or current alcohol dependence ($n = 70$/group; Anderson et al. 2009). Modafinil or placebo was to be taken as a daily dose for 12 weeks. All study participants received a manual-driven cognitive behavioral therapy. The primary outcome measure was the change in average weekly cocaine nonuse days across the study weeks, analyzed by a general estimating equations (GEE) approach.

There was no difference in cocaine usage across the three study groups by the GEE analysis. The study also replicated the analysis used by Dackis et al. (2005) wherein missing urines were counted as positive for cocaine. This analysis also did not reveal a treatment effect favoring the modafinil groups. A secondary analysis of participants who did not have an alcohol dependence history or current alcohol dependence ($n = 125$) revealed a significant increase ($p = 0.02$) in cocaine nonuse days for the 200 mg (8.9 %) and 400 mg (8.5 %) modafinil groups relative to placebo. These non-alcohol-dependent modafinil subgroups also had a greater number of consecutive nonuse days, relative to the placebo group ($p = 0.01$). Craving was reduced in the 200 mg modafinil group although the effect was not statistically significant when corrected for multiple comparisons.

The second trial was a randomized, double-blind placebo-controlled trial of 210 cocaine-dependent participants who were randomized to a 200 mg modafinil ($n = 65$), 400 mg modafinil ($n = 70$), or a placebo group ($n = 75$) (Dackis et al. 2012). Unlike the Anderson et al. 2009 trial, prospective participants were excluded if they had any other drug dependencies. Thus, this group was a better match for the patient population from the first Dackis et al. (2005) study. The primary outcome variable was cocaine abstinence inferred by urine drug screens. Missing urines were imputed as positive. Other outcome measures assessed were withdrawal signs and symptoms, cocaine craving, and study retention.

There were no significant differences in cocaine abstinence across the three groups. The only trend ($p = 0.06$) seen favoring modafinil was in males in the 400 mg group versus males receiving placebo. There were no significant differences across groups on the other variables of interest.

The results of these two studies must be viewed as a disappointment as neither provided a robust signal of efficacy. It is conceivable that a combined analysis of these data sets could boost the power to determine differences across treatment groups.

41.2.4 D3 Dopamine Receptors and Buspirone

D3 dopamine receptors are located in limbic areas associated with cue- and drug-induced drug reward (Micheli and Heidbreder 2008). Cocaine produces an increase in D3 receptor mRNA and D3 receptor density in the rodent brain. Increases in D3 mRNA and receptors have been reported following cocaine cue-induced locomotion in mice (Le Foll et al. 2002) and a course of cocaine self-administration in rats (Neisewander et al. 2004). Upregulation of D3 mRNA (Segal et al. 1997) and D3 receptors have been reported in cocaine overdose fatalities (Staley and Mash 1996). These cocaine-induced neurobiological changes in D3 receptor density (and presumably, sensitivity to dopamine) may be a major determinant of cocaine-seeking behavior, in that they may enhance the reinforcing effects of cocaine use. D3 dopamine antagonists can block cue-induced, drug-primed, and stress-induced reinstatement of cocaine self-administration in rodents (Heidbreder 2008).

Buspirone has effects at multiple dopamine receptors. In vitro tests showed it to be a potent D3 dopamine receptor antagonist and a moderate D2 dopamine partial agonist (Toll et al. 2008) and a D4 antagonist (Bergman et al. 2013). Its D3 antagonist activity is in the same nanomolar range in in vitro tests as its well-known 5HT 1A activity. Buspirone has also been shown to reduce cocaine self-administration in high-grooming rats in a progressive ratio schedule (Homberg et al. 2004) and to block stress-induced (Beardsley et al. 2010) and cue-induced reinstatement (Shelton et al. 2013) of cocaine intake in cocaine-trained rats. Acute buspirone dosing (0.032 mg/kg) reduced cocaine self-administration in rhesus monkeys (Bergman et al. 2013). Further experiments by this same group showed that chronic buspirone dosing (0.32 mg/kg/h, i.v.) significantly reduced cocaine self-administration and shifted the dose-response curve downward in rhesus monkeys (Mello et al. 2013). Thus, preclinical data suggest that buspirone's blockade of D3 dopamine receptors would be a reasonable test of the hypothesis of an effect of D3 receptor blockade on cocaine abuse in humans.

Buspirone has been tested in two small studies of cocaine abusers ($n = 32$; Giannini et al. 1993) and ($n = 18$; Moeller et al. 2001). Giannini et al. evaluated cocaine withdrawal. Buspirone has also been given to 18 methadone-maintained patients in which reduction of drug use was evaluated (McRae et al. 2004), although cocaine use was not specifically reported. None of these studies had sufficient power to detect an effect associated with buspirone administration. The NIDA Clinical Trials Network is currently running a pilot study of the safety and efficacy of buspirone (60 mg/day) for the treatment of cocaine dependence (Winhusen et al. 2012).

41.2.5 Medications for the Treatment of Amphetamine/ Methamphetamine Dependence

Two clinical trials have been conducted that suggest bupropion can reduce methamphetamine use in light users (Elkashef et al. 2008; Shoptaw et al. 2008). Both of these studies evaluated 150 mg bid versus a placebo. Although the primary endpoint of statistically significant reduction of methamphetamine use was not achieved in either study, Elkashef et al. showed that bupropion significantly reduced methamphetamine use ($p < 0.001$) in light to moderate users (1–18 days of use per month at baseline). Similarly, Shoptaw et al. reported that bupropion also significantly reduced methamphetamine use ($p < 0.001$) in light methamphetamine users (defined as having 0–2 positive urines uses out of a possible six during the baseline period). McCann and Li (2012) conducted an analysis of individuals within groups who achieved multiple weeks of abstinence. In this analysis, bupropion significantly facilitated abstinence ($p = 0.0176$). Brensilver et al. (2012) reanalyzed the data on light to moderate users in the Elkashef et al. and Shoptaw et al. trials. These authors concluded that the inability to achieve at least three methamphetamine negative urine samples predicted a greater than 90 % likelihood of treatment failure. Thus, the primary trials and their reanalyses

suggest a patient population that may be responsive to bupropion and the time frame that at least a partial response should be seen.

Methylphenidate has been evaluated as a treatment agent for amphetamine dependence in a study in Finland (Tiihonen et al. 2007). In this study 53 intravenous amphetamine users were randomized to aripiprazole (15 mg/day), methylphenidate (54 mg per day), or placebo. The medication portion of the trial was 20 weeks. The primary outcome measure was amphetamine use as measured by urine toxicology. There were fewer amphetamine positive urines in the methylphenidate-treated group.

A follow-up trial to assess the efficacy of extended-release methylphenidate was conducted in Finland and New Zealand (Miles et al. 2013). Seventy-nine participants were randomized to either the methylphenidate (54 mg/day) or placebo group. The trial duration of 20 weeks was identical to the initial Tiihonen et al. (2007) study. There was no difference seen in amphetamine use between the two groups although retention was superior in the methylphenidate group ($p < 0.05$).

Naltrexone (50 mg/day, po) was found to reduce relapse in amphetamine-dependent trial participants (Jayaram-Lindstrom et al. 2008). Although no direct confirmatory trials have been reported in the extant literature, there are two publications that utilized naltrexone implants. The first was a study that randomized 100 amphetamine and opiate dually dependent participants to a naltrexone or placebo rod (Tiihonen et al. 2012). The primary outcome variables were urines negative for amphetamine and opiates and retention in the study. Missing urines were imputed as positive for the analysis. The naltrexone group had more drug-free urines (38 %) versus the placebo group (16 %) ($p = 0.01$). The number of amphetamine free urines was not statistically different across groups in a weekly drug use analysis. However, the number of times used per week was almost statistically significant ($p = 0.06$) with less days of use in the naltrexone group. Retention was greater in the naltrexone group ($p = 0.01$). Kelty et al. (2013) conducted a retrospective review of amphetamine-dependent users who were treated with naltrexone implants in Australia. Forty-four patients who received naltrexone implants gave self-report data on their amphetamine use. Almost 70 % claimed to be abstinent for at least 1 month. Of the 29 patients claiming abstinence at 1 month, 14 claimed to be abstinent at 6 months. The authors correlated abstinence with naltrexone blood levels and reported a direct relationship between blood levels and abstinence: those with a blood level greater than 2 ng/mL, 1–2 ng/mL, and less than 1 ng/mL had reported abstinence rates of 91 %, 43 %, and 39 %, respectively. Future trials need to incorporate urinalysis confirming abstinence with blood levels above 2 ng/mL as a threshold target in future trials.

Elkashef and colleagues (2012) evaluated the potential efficacy of topiramate versus placebo in the treatment of methamphetamine dependence in a randomized, double-blind, multicenter trial. One hundred forty methamphetamine-dependent adults received topiramate in a titrating dose schedule. The initial dose of 25 mg per day was ramped up to a maximum of 200 mg per day by the end of week 6. Doses were then kept constant for the next 6 weeks. The primary outcome measure was negative "methamphetamine use week" during weeks 6–12, analyzed using a GEE method.

There were no differences in methamphetamine use in weeks 6–12 across the two groups. However, when those participants in each group whose last baseline urine before randomization was negative ($n = 13$ in both the topiramate and placebo groups) were analyzed, the topiramate group had less methamphetamine use ($p = 0.02$). This finding suggests that topiramate should be reevaluated as a relapse prevention agent in methamphetamine-dependent populations (Vocci 2012).

41.2.6 Medications for the Treatment of Opioid Dependence

Buprenorphine and buprenorphine/naloxone prescribing have been increasing in the United States since their approval in October 2002. In fact, buprenorphine/naloxone was the 36th highest prescribed medication in the United States in 2012 with sales of nearly 1.5 billion dollars (Drugs.com 2013). The success of buprenorphine and buprenorphine/naloxone has not only engendered the development of generic dosage forms for these medications but also new dosage forms that have advantages in terms of diversion potential (Dasgupta et al. 2010). The first of these dosage forms is Probuphine, an implantable rod (26 × 2.5 mm) containing 80 mg of buprenorphine per implant. White et al. (2009) explored the efficacy, pharmacokinetics, and safety of switching 12 opioid-dependent study participants maintained on sublingual buprenorphine to the buprenorphine implant. Participants maintained on an 8 mg dose of sublingual buprenorphine received two rods while those on 16 mg of sublingual buprenorphine received four implanted rods in the subdermal space. The participants were followed for 6 months. Opioid withdrawal was assessed by the Subjective Opioid Withdrawal Scale (SOWS) and the Objective Opioid Withdrawal Scales (OOWS). Craving was assessed by the use of a Visual Analog Scale. Scores on the SOWS and OOWS were minimal; e.g., the SOWS score averaged over the 6 month period was 0.97 ± 2.18 (note the scale has a maximum score of 64). Craving scores were also minimal, averaging 2.25 ± 6.44 over the 6-month period (note the scale has a maximum score of 100). Three participants in the two implant group and two participants in the four implant group received sublingual buprenorphine as a rescue medication for withdrawal for an average of 4.8 ± 5.1 days.

The percentage of opioid-free urines during this pilot study (59 %) was consistent with results previously reported (60 % opioid-free urines) in a 6-month buprenorphine study by Pani et al. (2000).

No serious adverse events occurred in the group. Seven participants reported adverse events associated with implantation or removal of the rods. Five of the 12 participants experienced adverse events that were attributed to Probuphine: dizziness ($n = 3$), constipation ($n = 2$), and abdominal pain, implant site reaction, flushing, and pallor ($n = 1$).

Plasma samples were obtained over the 6-month period for determination of buprenorphine levels. The four implant group had an average plasma level of buprenorphine of 0.72 ± 0.11 ng/mL, essentially equivalent to the trough level

seen during the screening period when buprenorphine dosing was administered sublingually (0.72 ± 0.30 ng/mL). The terminal plasma half-life of buprenorphine post-removal of the implants was 23.8 ± 8.6 h.

A multicenter trial of the buprenorphine implant was performed in 18 centers in the United States (Ling et al. 2010). One hundred sixty-three male and nonpregnant female opioid-dependent study participants were randomized under double-blind conditions to the buprenorphine rods (four implants) or placebo (four implants) in a 2:1 ratio. All study participants were inducted onto 12–16 mg of sublingual buprenorphine and had to be maintained at that dose for 3 days before randomization.

In this trial supplemental sublingual buprenorphine, up to 12 mg, was allowed if participants experienced significant withdrawal or craving. An additional implant was also permitted if participants required supplemental buprenorphine more than 3 days in 1 week or 8 days over a 4-week period. Sixty-four of the 108 buprenorphine-implanted participants received supplemental buprenorphine for a median time of 7.5 days, whereas 91 % of the placebo group was supplemented with buprenorphine for a median time of 19.5 days during the first 16 weeks. The implants were removed after 6 months.

In addition to urine toxicology to determine opiate use, the Clinician Opiate Withdrawal Scale (COWS), the SOWS, a visual analog scale for craving, and Clinical Global Impression Severity (CGI-S) and Improvement (CGI-I) were obtained at baseline, 16 and 24 weeks.

Participants in the buprenorphine implant group used less opiates (40.4 % opiate negative versus 28 % negative in the placebo group) as measured by urine toxicology results ($p = 0.04$). Additionally, the buprenorphine implant group had lower scores on the COWS ($p < 0.001$), SOWS ($p = 0.004$), and the visual analog craving scale ($p < 0.001$). Lower scores were recorded in the buprenorphine group on the CGI-S ($p < 0.001$) with a corresponding improvement on the CGI-I scale ($p < 0.001$). Retention favored the buprenorphine implant versus placebo groups with 67.5 % and 30 % retention, respectively ($p < 0.001$).

Two serious adverse events (SAEs) were reported in the buprenorphine group and four were reported in the placebo group. One of the SAEs in the buprenorphine group was thought to be possibly treatment-related: one participant with a history of chronic obstructive pulmonary disease and embolism experienced an exacerbation of these conditions. One placebo participant developed a cellulitis at the implant site that required hospitalization, debridement, and drainage. The other SAEs in either group were not treatment-related. Most of the adverse events in the buprenorphine group were implant site-related; three participants discontinued due to implant site pain ($n = 1$) or pain and infection ($n = 2$). No placebo participants discontinued due to adverse events.

A second, multicenter trial of the buprenorphine implants was conducted in 20 sites in the United States (Ling and Beebe 2013). Opiate-dependent, adult males and nonpregnant females ($n = 287$) were randomized in a double-blind fashion to a buprenorphine implant group (four implants) or a placebo group (four implants) and a sublingual buprenorphine group in an open-label fashion. The primary

outcomes were the comparison of the two implant groups and the comparison of the buprenorphine implant group to the open-label buprenorphine/naloxone group.

At the conclusion of the 6-month trial, all study completers were allowed to enroll in a 6-month open-label extension of the buprenorphine implants.

In the comparison of the implant groups, the buprenorphine implant group had a greater percentage of opiate negative urines ($p < 0.0001$) and greater retention (64 % vs. 25 %, $p < 0.0002$). The implant group response was also shown to be non-inferior to the sublingual buprenorphine group response at a pre-specified non-inferiority level of −15 %.

A long-acting, injectable preparation of buprenorphine is being developed by Camurus (2013). Depending on the lipid composition of the controlled-release matrix, an injection could produce therapeutic blood levels last for 1 week or 1 month. A safety, efficacy, and pharmacokinetics study of the 1-week preparation in 41 opiate-dependent individuals was reported on the company's website. Dose-proportional and dose-linear kinetics were observed after a single injection of buprenorphine (CAM2038). SOWS and COWS assessments were "well controlled for up to 10 days after single dose injection of CAM2038." These results obviously need to be published in a peer-reviewed journal but, if verified, would give clinician's another option to treat opioid dependence with minimal concern about diversion.

Methadone is available as a racemic mixture for treatment of opioid dependence. Besides an effect on respiratory depression, racemic methadone has effects on cardiac repolarization by virtue of its ability to block the inwardly rectifying K^+ channel (IKr) in the myocardium. The human ether-a-go-go-related (HERG) gene encodes the potassium channel current. Methadone blocks the HERG channel at Cmax concentrations seen in human populations (Katchman et al. 2002). The delayed repolarization produced by methadone (and other medications that block the IKr channel) results in a prolongation of the QT interval in the ECG. There are numerous case reports in the literature of methadone's ability to prolong the QT interval (Andrews et al. 2009) along with cohort studies (Maremmani et al. 2005; Ehret et al. 2006; Fanoe et al. 2007). The QT interval associated with chronic methadone treatment at a fixed dose has been reported to increase (Andrews et al. 2009). Martell et al. (2005) reported that methadone increased the QTc by an average of 12 ms and the increase was correlated to both trough and peak methadone serum levels. Roy et al. (2012) reported that 11.1 % of 180 patients enrolled in a methadone clinic had QTc intervals greater than 450 ms. In the cohort reported by Ehret et al. (2006), 16 % of the group has a QTc >500 ms, and 3.6 % developed torsades de pointes (TdP). Fanoe et al. (2007) calculated that each 1 mg increase in methadone dose increased the QTc by 0.14 ms. Thus, methadone may produce toxicity through both respiratory and cardiac mechanisms (QT prolongation that could lead to TdP).

The R-isomer (l-methadone or levomethadone) has been reported to be ten times more potent at mu receptor binding sites than the S-isomer (Kristensen et al. 1995) and twice as potent as racemic (R,S) methadone. The S-isomer has been reported to be 3.5 times more potent than the R-isomer in blocking the HERG channel (Eap et al. 2007). Thus, the S-isomer is likely to be a greater contributor to QT prolongation than the R-isomer when the racemic mixture is given. In 39 patients

receiving R,S-methadone for treatment of opioid dependence, Ansermot and colleagues (2010) reported the QT interval was significantly reduced by 3.9 ms per week when the patients were switched to a half-dose of the R-isomer ($p = 0.04$). Verthein and colleagues (2005) enrolled 75 patients to test the hypothesis that switching from R-methadone to R,S-methadone was associated with more withdrawal symptoms and side effects than switching from R,S-methadone to R-methadone. These investigators employed a stratified, randomized, 2 × 2 cross-over study design over a period of 8 weeks. Every second patient was switched from the pre-study medication to the other medication and the switched back after 4 weeks of dosing. Although no significant differences in withdrawal symptoms or side effects were noted between the two medications, patients treated with l-methadone reported fewer withdrawal symptoms. An open-label substitution of R-methadone for the (R,S) methadone in a multi-clinic setting, at half the dose of the R, S mixture, resulted in successful transition to the R-isomer in 91.8 % of the 1,552 study participants (Soyka and Zingg 2009). Less than 1 % of the patients dropped out due to adverse events. Moreover, patients switched to the R-isomer for 4 weeks reported fewer withdrawal symptoms ($p < 0.001$), less craving (reduced from 69.3 % to 36.8 % of patients reporting craving), fewer side effects ($p < 0.001$), and less illicit drug use. In fact, 98 % of the patients did not report any side effects. The number of illicit drug screens dropped from 61.2 % prior to transfer to 39.8 % 4 weeks after the switch to R-methadone. Compliance with R-isomer treatment was rated as "very good" or "good" for 85.8 % of the patients compared to 60.1 % prior to the switch ($p < 0.001$). Seventy-nine percent of the participating clinicians felt that the R-isomer was tolerated by the patients "better" or "much better" and only 1 % of the clinicians felt that the patients tolerated the R-isomer "worse" or "much worse" than the R,S-racemate. These data suggest the following benefits of R-methadone compared to the R,S-racemate: (1) lesser degree of QT prolongation with a lesser propensity for development of TdP, (2) better management of withdrawal symptoms, (3) less craving for opiates, (4) less illicit drug use, (5) fewer side effects, and (6) greater compliance with the treatment regimen. Thus, a rational strategy to reduce the morbidity and mortality of methadone is to switch patients who are on the racemate to the levo-isomer.

Currently, the R-methadone is only marketed in Germany and Austria. Consideration should be given to expanding the availability of this medication.

41.3 Conclusion

Gabapentin, pregabalin, sertraline, and ondansetron have demonstrated efficacy for the management of alcohol dependence. The efficacy of gabapentin has been confirmed in several studies; a posttreatment effect slowing the onset of return to heavy drinking has been seen in two studies (Brower et al. 2008; Anton et al. 2009). Although confirmatory studies will be needed for pregabalin, sertraline, and ondansetron, the alcohol treatment field has reason to be optimistic about this group of medications.

Gabapentin and nabilone have emerged as possible pharmacotherapies for the management of cannabis dependence. These findings are relatively new and require confirmation in the case of gabapentin and determination of efficacy in at least two phase II trials for nabilone.

The amphetamine salts and topiramate combination for the treatment of cocaine dependence needs confirmation in a longer clinical trial. Although the 3 weeks of continuous abstinence is a clear signal of efficacy that merits publication in the literature, FDA regulatory authorities want trials of 6-month duration with abstinence measured at the end of the trial to demonstrate efficacy (Winchell et al. 2012).

The potential efficacy of buspirone is now being investigated in a clinical study (Winhusen et al. 2012). Studies performed in rats (Beardsley et al. 2010; Shelton et al. 2013) and rhesus monkeys (Bergman et al. 2013; Mello et al. 2013) give a solid rationale for testing buspirone in cocaine dependence. Any studies performed with buspirone should measure plasma levels so that adherence can be measured and the levels can be compared to plasma levels in rhesus monkeys that suppressed cocaine self-administration (Mello et al. 2013).

New medications in testing for the treatment of opioid dependence are currently variations on a theme. Longer-acting dosage forms of buprenorphine reduce the risk of diversion and, in the case of the implant, appear to be equally efficacious to sublingual buprenorphine/naloxone. These medications may be particularly useful in nonadherent patient populations and in rural areas where patients have to travel great distances to receive medical care. The development of R-methadone would likely be a safer version of methadone administration with equal efficacy to the racemic mixture (Soyka and Zingg 2009).

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Evaluating the Therapeutic Utility of Hallucinogens for Substance Use Disorders

42

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Contents

Abstract

Hallucinogens represent a promising but controversial treatment for substance use disorders. Research into their efficacy and clinical feasibility has been hampered, however, by legal, cultural, and political restrictions since the late 1960s, when many of these substances were criminalized. In light of these substantial limitations, this chapter evaluates what is known about the uses of hallucinogens in the treatment of substance use disorders. First, the neurobiological and psychoactive effects of hallucinogens are summarized. The relevance

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of these effects to therapeutic mechanisms is explored, with special attention given to recent findings that elucidate the prefrontal effects of hallucinogens. Set and setting are defined and discussed, and consideration is given to how the cultural use of hallucinogens, in developed as well as preindustrial societies, can inform how they might be used appropriately in medical settings. A variety of hallucinogen-oriented therapeutic strategies are reviewed, including behavioral, psychedelic, psychodynamic, and neurobiological models. A review of the available research subjects that while the therapeutic utility of hallucinogens may be highly promising, the evidence is far from conclusive. The chapter concludes with a discussion of future directions for research.

42.1 Introduction

Like heroin, hallucinogens were initially regarded as possible medicines before concerns over their risks led them to be classified as nontherapeutic drugs of abuse. Unlike heroin, however, hallucinogens have demonstrated therapeutic feasibility, as well as safety and tolerability, in various treatment contexts (Bakalar and Grinspoon 1997; Galanter and Kleber 2008; Malleson 1971). Numerous case studies and several controlled trials have suggested that classical hallucinogens, and specifically lysergic acid diethylamide (LSD), can be administered in appropriate therapeutic settings to certain psychiatric populations, such as alcohol-dependent or depressed individuals, with minimal risk and with apparent benefit (Malleson 1971; Vollenweider and Kometer 2010). Given these promising findings, it is important to understand how these compounds came to be classified as dangerous drugs of abuse with no medical value. This will provide some background to the deficits in our knowledge concerning their therapeutic utility.

Believed at one time to herald a new paradigm in the treatment of mental illness (Hoffer 1970), but criminalized in most Western countries in the late 1960s and early 1970s due to reports of widespread misuse and abuse (Leuner 1994), hallucinogens have for decades now been condemned by mainstream psychiatry as too high risk to merit further investigation. Accordingly, funding for clinical research with classical hallucinogens had rapidly dwindled in the late 1960s from millions of dollars annually in the United States alone, despite promising early findings, particularly with severe alcoholism (Bakalar and Grinspoon 1997; Leuner 1994). This abrupt halt to clinical research has left many important questions unanswered and has severely restricted our capacity to appropriately assess their clinical effectiveness.

In light of these limitations, this chapter reviews what is known about the uses of hallucinogens in the treatment of substance use disorders. First, we summarize the neurobiological and psychoactive effects of hallucinogens, and provide a brief overview of the various cultural contexts in which their use has occurred. Then, we explore several models proposed for how they might be effective for substance use disorders and examine the research conducted to date assessing their therapeutic

efficacy. When appropriate, popular preconceptions about these compounds, pertaining to both possible risks and benefits, are evaluated based on the available evidence. We conclude with a discussion of future directions for clinical research.

42.2 Classifications, Properties, and Historical Uses

42.2.1 Classifications and Mechanisms

The term "hallucinogen" designates a diverse group of substances whose primary effects are changes in perception, experience, and consciousness comparable to the alterations that characterize non-ordinary mental states such as dreaming, meditation, psychosis, dissociation, or mystical experience (Galanter and Kleber 2008; Vollenweider and Kometer 2010; Hoffer 1970). It is worth noting that hallucinogens, despite their name, rarely engender hallucinations (or sensory phenomena that are experienced as real though lacking a referent in reality). This has led other names to be proposed for this drug class, such as psychedelic (mind manifesting), phantasticant (inducing fantasy), and oneirogen (dream generating). Hallucinogen (from the Latin *alucinor*: mental wandering or dreaming) remains the most widely used term for these substances in medical settings, and we will employ it here, despite its limitations.

Hallucinogens encompass many distinct substances, some with quite different neurobiological and psychoactive effects. These various agents can be organized either by their immediate neurobiological effects or by their molecular structure. The two broadest molecular subgroups are the indoleamines and phenethylamines (Fig. 42.1). The indoleamines include LSD, dimethyltryptamine (DMT), psilocybin, ibogaine, and harmaline. Phenethylamines include naturally occurring compounds such as mescaline but also an ever-expanding number of synthetic compounds, e.g., 2-CB, MDMA, MDA, and DOM.

Classical hallucinogens are widely believed to exert their psychoactive effects by direct agonism of the 5HT2A serotonin receptor, though other serotonin receptors may also be involved. Classical hallucinogens include psilocybin, LSD, mescaline, and DMT. These compounds, though sharing neurobiological activity, come from quite diverse sources: psilocybin can be isolated from a mushroom, for example, and mescaline derives from a cactus in the American Southwest.

Hallucinogens may also exert their psychoactive effects by *nonclassical* mechanisms. These mechanisms include serotonin release or nonspecific serotonin receptor activation, as in the case of MDMA ("Ecstasy" or "Molly") and other phenethylamines; *N*-methyl-D-aspartate receptor (NMDAr) or glutamatergic modulation, as with ketamine and phencyclidine; cannabinoid receptor activation; and κ-receptor agonism, as occurs with *salvia divinorum*. These mechanisms are by no means exhaustive; there are other compounds (e.g., nitrous oxide, the fly agaric mushroom) that work by different mechanisms (Bakalar and Grinspoon 1997; Galanter and Kleber 2008; Malleson 1971). Interestingly, recent research suggests that classical hallucinogens and dissociative anesthetics, despite their apparent

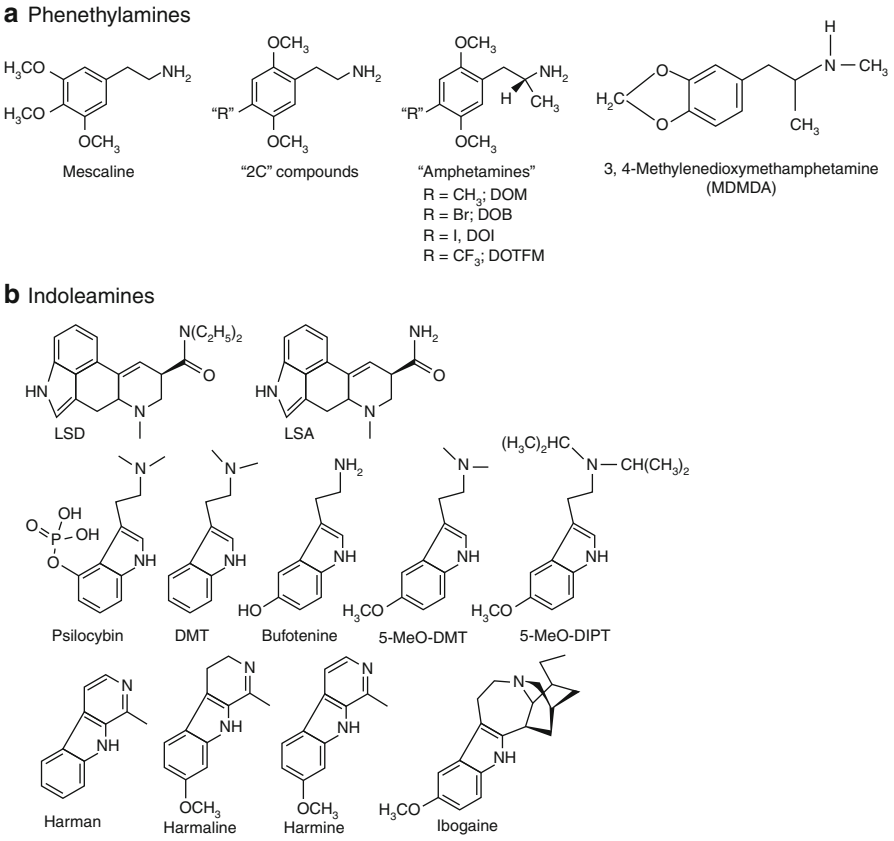

Fig. 42.1 Hallucinogens by molecular group

differences in immediate neurobiological activity, work by a common final pathway of prefrontal glutamatergic modulation (Vollenweider and Kometer 2010).

The effect of classical hallucinogens on cerebral blood flow (CBF) and brain activity is currently a matter of some controversy. Previously demonstrated to increase blood flow to and activity in the prefrontal areas when administered orally (Vollenweider and Kometer 2010; Schreckenberger et al. 1998; Gouzoulis-Mayfrank et al. 1999), recent research by a single group has suggested that psilocybin may *decrease* CBF to certain prefrontal areas by functional magnetic resonance imaging (fMRI), when administered as a bolus dose by the intravenous (IV) route, as well as reduce prefrontal activity (Carhart-Harris et al. 2012b). These changes in CBF and activity appear to correlate with certain psychoactive effects. Further, IV psilocybin has been shown by the same group to attenuate functional connectivity, synchronize anti-correlated networks, and reduce resting-state default mode network (DMN) activity, which is thought to correspond to self-referential processing and the structuring of experience (Carhart-Harris et al. 2012a, b). These latter effects on the DMN

and functional connectivity are consistent with brain activity associated with other altered states, such as meditation and psychosis, as well as with the subacute effects of sub-anesthetic ketamine (Scheidegger et al. 2012). The diminution in prefrontal CBF and activity found with IV psilocybin, however, has yet to be replicated by other groups. It is also unclear whether this effect on CBF is indeed crucial to the psychoactive effects of psilocybin or whether it is an epiphenomenon of tryptamine-like vasoconstriction.

42.2.2 Psychoactive Properties and Risks

The psychoactive effects of hallucinogens can be markedly different depending on the type of drug and its route of administration. Even agents from the same subgroup (e.g., mescaline and MDMA) can be quite dissimilar. Here, we will aim to describe all *potential* hallucinogenic effects. Classical hallucinogens are the subgroup that typically exhibits the widest range of these alterations (Bakalar and Grinspoon 1997; Galanter and Kleber 2008; Malleson 1971; Vollenweider and Kometer 2010).

Hallucinogenic alterations can be grouped into three categories, all of which can be experienced concurrently (Vollenweider and Kometer 2010; Studerus et al. 2011). The first and most basic are *perceptual changes*. These include an intensification of sensory phenomena; greater sensitivity to latent phenomena (e.g., patterns or textures that are ordinarily overlooked); changes in the perception of time or space; conflation of sensory modalities, as in synesthesia; the production of eidetic imagery, such as spirals, shapes, and arabesques; greater aesthetic appreciation; illusions; pseudohallucinations (with intact reality testing); and an altered sense of the body.

The second category of alterations is *experiential*. These changes include alterations in mood (euphoria, hilarity, terror, or anxiety), altered relatedness to others or to objects (empathy, alienation, connectedness, or merging), philosophical/existential concerns, increased insight, dissociation, emergence of pseudo-delusional or overvalued ideas (e.g., the world will end in the near future), suggestibility, and a reliving of past memories or a resurgence of apparently resolved conflicts.

Mystical or transpersonal experiences constitute the third category. These are alterations characterized by heightened spirituality or mysticism, similar to experiences described by mystics, philosophers, or religious figures in historical accounts. They can include a struggle or conflict of archetypal dimensions; a sense of life's absurdity or lack of purpose; an experience of complete oneness with all that is; near-death or birth-like experiences; immersion in a total void; ego diffusion, as in so-called oceanic boundlessness; ego dissolution; a sense of the sacred; spiritual ecstasy; spatiotemporal transcendence; nondiscursive or ineffable understanding (e.g., knowledge beyond the pale of language); overwhelming sense of finiteness or sinfulness; identification with the divine; reincarnation; reevaluation of values; redemption; and metaphysical/cosmological speculation. Recent research with psilocybin suggests that the personal significance of such experiences can be enduring,

with individuals continuing to report 1 year later that the experience was among the most important in their lives (Griffiths et al. 2006, 2008).

As we will see later, these various alterations in consciousness are believed by some treatment models to serve as the psychological mechanisms by which clinical improvement for addictive disorders occurs. However, these same alterations also represent the greatest source of toxicity, especially when the hallucinogen is consumed by unprepared or unstable individuals, or in the absence of a supportive, responsive framework. In such circumstances, hallucinogens may lead to acute behavioral disturbances or persistent distress that may require emergency treatment. Common adverse effects of hallucinogens include anxiety or dysphoria, generally circumscribed to the period of intoxication; loss of behavioral control during acute intoxication, including passivity, disorganization, indecision, and suboptimal functioning; and more rarely, precipitation of persistent anxiety, affective, or psychotic disturbances in vulnerable individuals (Bakalar and Grinspoon 1997; Vollenweider and Kometer 2010; Johnson et al. 2008; Imperi et al. 1968).

The criminalization of hallucinogens was buttressed by various claims of risk that are now recognized as false, but which have managed to persist despite no supportive evidence (Bakalar and Grinspoon 1997). These unsubstantiated claims include concerns that classical hallucinogens cause chromosomal damage (Cohen and Shiloh 1977–1978); that they lead to suicide, murder, or debauchery, even when used in appropriate clinical settings (Malleson 1971; Studerus et al. 2011); or that they engender schizotypal personality changes or lasting psychotic disturbances in individuals without a preexisting vulnerability (Malleson 1971; Studerus et al. 2011; Vardy and Kay 1983).

Though hallucinogens may be used irresponsibly or abused (e.g., repeatedly ingested despite the emergence of behavioral distress or other adverse effects), classical hallucinogens do not present a risk for dependence according to animal models; they are not self-administered, do not create conditioned place preference or physiological dependence, and do not lead to dopamine release from reward pathways (Fantegrossi et al. 2008).

Recent polls in the United States parallel these findings and strongly suggest that hallucinogens are infrequently used and do not create dependence phenomena. Hallucinogens are used most commonly in late adolescence and young adulthood, with up to 11 % of 12th graders having used at least once, and their use is generally sporadic, clustered, or infrequent. Even heavy users do not use more than two or three times a week, and it is uncommon for hallucinogen use to persist beyond young adulthood. Barring atypical substances such as ketamine, nitrous oxide, certain phenethylamines (i.e., MDMA), and cannabis, hallucinogens do not create physiological dependence or tolerance, and dependence phenomena, such as an inability to stop using, are rarely seen (Galanter and Kleber 2008; Fantegrossi et al. 2008; Passie et al. 2002).

Research suggests that the behavioral and psychoactive risks associated with hallucinogens may be effectively minimized and managed by the context in which the agents are administered. It has been recognized that hallucinogenic alterations are shaped, to an extent, by the past experience, expectations/intentions, preparation,

and attributes of the individual (the *set*), as well as by the context (including other individuals, medical staff, or a guide) in which the experience occurs (the *setting*) (Bakalar and Grinspoon 1997; Malleson 1971; Vollenweider and Kometer 2010; Imperi et al. 1968; Studerus et al. 2012). The set and setting may play a primary role in whether the hallucinogen experience is pleasant and enriching or dysphoric and upsetting. Most importantly, the set and setting also constitute the most salient modifiable variables affecting whether or not hallucinogen-related toxicity occurs. Many reports from the heyday of hallucinogen research – the 1950s and 1960s – have consistently shown that with appropriate patient selection, preparation, guidance, and follow-up care, hallucinogens can be safely administered in medical settings, with minimal reports of behavioral toxicity or persistent adverse effects (Bakalar and Grinspoon 1997; Malleson 1971; Vollenweider and Kometer 2010; Studerus et al. 2011). Indeed, most accounts of behavioral toxicity or persistent distress occur outside of medical settings, when these substances are used irresponsibly. These findings are now being replicated by more recent investigations as human-oriented hallucinogen research carefully resumes (Johnson et al. 2008).

42.2.3 Historical Use

Set and setting also provide a valuable lens by which to understand the historical use of hallucinogens. As is the case with many psychoactive substances, hallucinogens have been accorded an important, and sometimes sacramental, place in various cultural traditions. The use of the hallucinogen might be ritualized or ceremonialized, symbolically integrated into the group's beliefs and traditions, or invested with supernatural importance (Fig. 42.2). The unique psychoactive profile of hallucinogens, and particularly their capacity to engender mystical-type experiences, has made them especially well suited to religious, initiation, or healing ceremonies (Bakalar and Grinspoon 1997; Hofmann and Schultes 1979).

Indigenous groups in the Americas have a robust and diverse history of incorporating hallucinogens into their rituals and ceremonies, likely because of the wealth of naturally occurring psychoactive substances in these continents. The Aztecs ritualized the use of psilocybin-containing mushrooms for millennia; peyote (mescaline) and salvia are used by groups in Mexico; and DMT, in the form of ayahuasca or yage, is central to Shamanic or religious ritual in various indigenous and syncretic Amazonian traditions. Despite DMT and mescaline being illegal in the United States, they can be licitly used in their naturally occurring forms by members of certain religions that are recognized by the US government as requiring these substances for proper worship. Of note, both DMT (as ayahuasca) and mescaline (as peyote) are used by their respective communities to promote health and address certain ailments, such as addiction. The spiritually oriented set and setting implicated in the therapeutic use of hallucinogens have led some researchers to propose that psychospiritual mechanisms account for their putative benefits. Researchers have accordingly proposed hallucinogen-based treatment models that aim to elicit mystical states similar to those cultivated in hallucinogen-oriented rituals (Bakalar and Grinspoon 1997;

Fig. 42.2 Various mushroom stones. These stones, dating from 1,000 BC to 500 CE, are approximately 1 ft in height. They suggest the religious and cultural importance accorded to psychoactive mushrooms by groups that consume them sacramentally, ritually, or ceremonially (Image adapted from *Plant of the Gods* by Schultes and Hofmann)

Hofmann and Schultes 1979). (These will be discussed in greater detail in the next section, alongside other hallucinogen-based treatment models.)

The widespread use of hallucinogens in the United States and Europe among the young during the 1960s is also worth discussing. Alongside being privileged for their potent ability to alter and enhance sensory experience, hallucinogens (and primarily LSD) were celebrated by the counterculture as tools for self-discovery, direct mystical communion, and transcendence from ordinary, consensus experience. This attitude towards hallucinogens, fueled by such popular figures as Aldous Huxley, Timothy Leary, and Alan Watts among many others, gained particular momentum in the context of the social problems and generational conflicts that characterized the late 1950s and 1960s, with many people, and particularly the young, disillusioned by the belligerent imperialism, consumerism, materialism, and conformity that had come to shape their societies. In this troubled time, hallucinogens came to represent, much as in some indigenous cultures, a means by which to access deeper truths and initiate communal renewal. Unlike these indigenous cultures, however, the United States and other Western countries lacked the cultural framework to effectively incorporate hallucinogen use, support those who sought to use them, and respond creatively to the powerful experiences occasioned by them. Instead, unsupervised and irresponsible use proliferated; traumatic or sensational adverse events made headlines; and the substances were condemned as dangerous and bereft of benefit. The importance of a supportive and guided framework that adequately screens and prepares the individual before hallucinogen administration

cannot be overstated and should guide both the clinical and cultural use of these compounds to minimize the risks associated with them, as well as optimize their benefits (Bakalar and Grinspoon 1997; Leuner 1994).

42.3 Hallucinogen-Based Treatment Models

The majority of addiction-oriented treatment models incorporating hallucinogens are aimed at utilizing their unique psychoactive effects for therapeutic ends. As the acute and downstream neurobiological effects of these agents have begun to be elucidated, new models have emerged that emphasize biological mechanisms of therapeutic efficacy. We will examine each of these models in turn.

42.3.1 Negative Reinforcement

The earliest hallucinogen-based model for the treatment of alcohol dependence in a medical setting originated with the observation that individuals who had undergone delirium tremens (DTs) were more likely to pursue abstinence from alcohol than those who had not (Bakalar and Grinspoon 1997; Hoffer 1970; Abramson 1967). It was also believed that hallucinogens can engender delirium and suffering, as well as nightmarish reflections on the ravages of alcohol, that were comparable in phenomenology to DTs. Thus, much like DTs, hallucinogen-generated suffering was thought to lead individuals to abandon drinking.

This model is predicated on the *negative reinforcement* hypothesis of learning, whereby a certain behavior is reinforced (such as maintaining abstinence) by the negative consequence that would occur if the behavior were *not* performed (such as a resurgence of DTs and alcohol-related distress). As such, a behavior comes to be performed in order to avoid a certain adverse outcome. Agents that were used in this model include antimuscarinic agents such as scopolamine and belladonna and LSD. The therapeutic framework was primarily oriented around accentuating the horrors of alcohol and shoring up motivation to stop using. A similar strategy was used in an early form of ketamine psychedelic therapy (KPT) wherein the horrors of the problem drug (alcohol or opioids) were reinforced using cues or props while the patient was actively intoxicated with a sub-anesthetic dose of intramuscular ketamine (Krupitsky and Grinenko 1997).

42.3.2 Psycholytic Therapy

Hallucinogens were believed to facilitate psychoanalysis by weakening ego defenses; increasing the capacity for free association and memory retrieval; and creating more detachment from habitual thought patterns. They were also believed to accelerate the interpretative process by heightening transference reactions and engendering fantasy and pseudo-dream states within the session (Fig. 42.3).

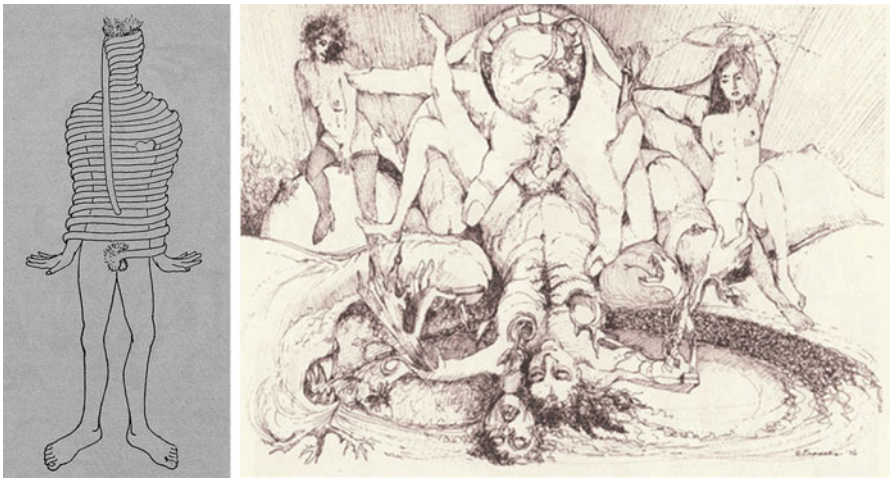

Fig. 42.3 These drawings by trained artists are visual representations of experiences that occurred during LSD-assisted psychotherapy. They demonstrate the psychological depth and intensity of the conflicts that might emerge during psychedelic experience, as well as how readily these conflicts might lend themselves to psychodynamic exploration. In these images, the artists may be depicting their conflicted attitude towards sexual desire, and anxieties about how sexual desire and union may threaten individual identity (Adapted from *LSD Psychotherapy* by Stanislav Grof)

LSD was thought to be most effective at a low dose for these purposes. The therapeutic framework was the typical one of psychoanalysis, with sessions occurring several times a week and with the analyst seated out of sight of the generally supine patient so as to facilitate transference reactions, free association, and fantasy. Frequency of LSD administration varied from a few times weekly to monthly, and the goal was to raise to conscious reflection the unconscious processes that perpetuate addictive behaviors. This model was primarily used, however, to address depressive and anxiety symptoms, not substance use disorders (Bakalar and Grinspoon 1997; Malleson 1971; Vollenweider and Kometer 2010; Hoffer 1970; Abramson 1967).

42.3.3 Psychedelic Therapy

Psychedelic therapy refers to the variety of therapies aimed at using hallucinogens to provoke "psychedelic" states and that provide a therapeutic framework to allow the individual to integrate the experience(s) into a healthier worldview and lifestyle. While the phenomenology of the target experience might vary – one approach might aim for a near-death experience, for example, while another a mystical communion with the cosmos – the common goal is to produce experience with potent *transformative* potential, such that it provides the patient with opportunity for existential reappraisal, a beneficial shift in perspective, and refreshed creativity. Such hallucinogen-based experiences are comparable to the mystical states occasioned

during the indigenous ceremonies discussed earlier. Furthermore, they are similar to the spontaneous experiences described by addicted individuals who undergo a transformative experience, be it "hitting rock bottom" or "having a moment of clarity," that serves to provide an experiential foundation for subsequent abstinence (Hoffer 1970; Abramson 1967; Krupitsky and Grinenko 1997; Miller and C'de Baca 2001).

Psychedelic therapy involves a high level of rapport, preparation, guidance, and post-session integration. It is typically carried out over many encounters, with several sessions occurring before the hallucinogen is administered so as to ensure that the participant is adequately prepared and comfortable with his/her treatment team. In current psychedelic therapy models, the team is generally composed of a male and female who engage with the patient as a dyad during the hallucinogen session. The role of the dyad is to provide gentle support and reassurance throughout the session, particularly when distressing phenomena may occur (Johnson et al. 2008).

Psychedelic therapy with high-dose LSD became the dominant hallucinogen-based model for treating alcohol dependence in the 1960s, and enough comparable controlled studies were completed as to produce sufficient data for a recent meta-analysis, which will be discussed later. KPT, mentioned above, was used in Russia in the 1980s and 1990s and was intended to trigger near-death and rebirth experiences with ketamine to treat opioid or alcohol dependence. Ibogaine is found in the root bark of an African shrub *iboga* and continues to be used by the Bwiti for healing, pleasure, initiation, and spiritual communion. Ibogaine as a treatment for opioid dependence emerged from the psychedelic/experiential model in the 1950s, but was investigated preclinically with government funding in the 1980s and 1990s with greater emphasis on neurobiological mechanisms. Ayahuasca (a brew composed of plants containing DMT and an MAOI, which serves to inhibit first-pass DMT metabolism) is beginning to be investigated in small pilot studies in Spain and Brazil for treating various addictive disorders. More recently, researchers in the United States are testing the feasibility of embedding psychedelic therapy using psilocybin in more conventional addiction-oriented therapies, such as cognitive-behavioral therapy (CBT) or motivational enhancement (ME), to treat nicotine and alcohol dependence (ClinicalTrials.gov Identifier: NCT01534494) (Bakalar and Grinspoon 1997; Malleson 1971; Hoffer 1970; Abramson 1967; Krupitsky and Grinenko 1997; Alper and Glick 2001).

42.3.4 Hallucinogen-Facilitated Therapies

Another emerging model involves utilizing hallucinogens to facilitate psychotherapies beyond psychoanalysis or the psychedelic framework. An ongoing controlled trial investigating sub-anesthetic ketamine and mindfulness training for cocaine dependence represents an example of this approach (ClinicalTrials.gov Identifier: NCT01535937). Other strategies might include embedding the hallucinogen in a framework of 12-step facilitation or group psychotherapy. The pilot studies with psilocybin mentioned above represent a mixed model where the psychedelic therapy is intended to produce a transformative experience that, in turn, leads to

increased engagement with more conventional addiction-oriented psychotherapies, such as CBT or ME.

42.3.5 Neurobiological Approaches

Recent research has served to clarify the neurobiological effects associated with hallucinogens and has broadened the scope of clinical research with these compounds by suggesting that they might target some of the neural, synaptic, or functional deficits associated with addiction as well as other psychiatric disorders. While classical hallucinogens and their nonclassical counterparts initiate their psychoactive effects by different mechanisms, they may have comparable downstream effects, particularly on prefrontal regions. These effects include the promotion of neural plasticity, improvement of prefrontal glutamate homeostasis, modulation of glutamatergic neurotransmission, attenuation of problematic cortical excitation, and regulation of DMN activity and functional connectivity (Vollenweider and Kometer 2010; Carhart-Harris et al. 2012a; Scheidegger et al. 2012). Many of these mechanisms have direct relevance to the deficits associated with substance use disorders.

Ibogaine was investigated in this way for opioid dependence, with the hypotheses that NMDAr effects were implicated in its anti-addictive properties and reduction in withdrawal symptoms (Vollenweider and Kometer 2010; Alper and Glick 2001). However, an analog iboga compound with less toxicity, 18-methoxycoronaridine (18-MC), has been found to exert comparable anti-addictive effects but with negligible NMDAr activity, suggesting that the main mechanism of action may not be what was thought previously (Glick et al. 2000). Similarly, the NMDAr antagonist ketamine is being investigated along neurobiological lines as a treatment for various substance use disorders.

42.4 Evidence for Efficacy

42.4.1 Clinical Evidence

Most of the clinical research conducted with hallucinogens for substance use disorders occurred in the 1950s and 1960s, focused on LSD for alcohol dependence, and lacked the rigorous design characteristics that have come to characterize modern research methodology. It is therefore not possible to draw conclusions from these early preliminary studies, though there may be some promising signals. A literature search, for example, reveals many clinical anecdotes, case studies, and trials of varying degrees of scientific rigor that suggest the feasibility of LSD as an antidipsotropic agent.

Case studies and open trials, however, cannot establish efficacy on their own. The gold standard in clinical research is widely recognized to be randomized controlled trials (RCTs). As such, a recent meta-analysis pooled results from seven comparable studies conducted in the 1960s that best approximate modern standards of RCT design (Krebs and Johansen 2012). The authors found that LSD,

at varying doses and in various psychotherapeutic contexts, was superior to the control conditions in promoting short-term abstinence. The authors note that while some of the analyzed trials were negative independently (perhaps because they were underpowered), the trials in aggregate demonstrated some promise. Without delving too deeply into a discussion of the study's limitations, it is important to emphasize that the favorable meta-analysis should not be interpreted to mean that LSD is effective for alcohol dependence, especially given the heterogeneity of study design, of population, and of LSD dosage in the analyzed trials. Research that adheres to rigorous and uniform randomized controlled design – employing effective blinding procedures, adequate controls, independent evaluations, appropriate outcome measures, and so on – is needed to clarify whether this promising intervention is indeed effective. Unfortunately, various legal and social obstacles make it unlikely that LSD will be investigated in a well-designed and adequately powered RCT in the near future.

Inconclusive evidence exists for other hallucinogens as well. Animal and preliminary human research indicated that ibogaine may be effective in reducing opioid self-administration and ameliorating withdrawal phenomena, but government funding stopped short of standardized clinical investigations due to concerns over its hallucinogenic effects and possible cardiotoxicity (Alper and Glick 2001). 18-MC, an iboga congener associated with less toxicity, has demonstrated promising effects on drug self-administration in animals, but has yet to be tested in humans. It is also unclear to what extent 18-MC has hallucinogenic properties, as its developers believe that its profile of neurobiological effects render it less likely than is ibogaine to produce alterations in consciousness (Glick et al. 2000). It is therefore unclear until it is tested in humans whether or not 18-MC should be grouped with hallucinogens.

Ketamine administered intramuscularly in the context of KPT has been found effective in preliminary controlled trials in producing abstinence from opioids and alcohol (Krupitsky and Grinenko 1997) and is currently being investigated, administered intravenously at sub-anesthetic doses for under an hour, as a treatment for cocaine dependence in individuals receiving mindfulness-based psychotherapy. There is insufficient evidence at present, however, to draw conclusions about the efficacy of ketamine for substance use disorders, even though it is one of the few hallucinogens, like LSD and ibogaine, that have been studied in RCTs for this purpose. This is in contrast to ayahuasca, psilocybin, and mescaline, for which only dramatic clinical anecdotes, community studies, and favorable open trials are available. Systematic RCTs need to be conducted in order to establish the efficacy of these promising compounds.

42.4.2 Mechanism-Oriented Evidence

In the absence of large-scale RCTs, researchers have turned to more modest laboratory studies to investigate how hallucinogens may impact on outcomes relevant to addiction. These studies have thereby sought to elucidate the

mechanisms by which hallucinogens, and ketamine and psilocybin in particular, might benefit substance use disorders. In a recent series of studies with healthy volunteers (Griffiths et al. 2006, 2008), orally administered psilocybin in the context of psychedelic therapy has been shown to occasion spiritually significant experiences whose importance persists up to 1 year after the session. Alongside being subjectively important to participants, these psilocybin-occasioned experiences may have been associated with increased openness, as assessed by a personality test (MacLean et al. 2011), and improved functioning, according to accounts of family and friends. These improvements appear to correlate with the mystical intensity of the experience, such that experiences were more likely to be associated with beneficial changes in character and functioning the more they approached a mystical state. These findings have some relevance to the management of substance use disorders in that they suggest that psychedelic experience leads to behavioral and characterological changes that might ameliorate addictive behaviors. These findings also appear to lend credence to the main hypothesis of psychedelic psychotherapy – namely, that psychedelic states may lead to beneficial psychological and behavioral effects. It remains to be determined, however, if psilocybin effectively produces such changes in addicted individuals.

Recent studies by several groups have shown that sub-anesthetic ketamine has powerful antidepressant effects that might implicate downstream mechanisms such as prefrontal neural remodeling and modulation of glutamate homeostasis (Mathew et al. 2012; Li et al. 2010). These findings are relevant to the management of substance use disorders insofar as addiction has been long recognized to involve glutamatergic prefrontal disruptions (Kalivas 2009; Goldstein and Volkow 2002; Kosten et al. 2006; Goldstein et al. 2007). These disruptions are thought to be associated with such deficits as the attenuated salience of natural rewards and increased sensitivity to stress and drug cues. Animal studies have further shown that glutamatergic modulators consistently decrease the reinforcing effects of powerful substances of abuse, such as cocaine, even as human studies with comparable glutamate-oriented compounds have been disappointingly unsuccessful (Collins et al. 1998; Bisaga et al. 2010). A recent laboratory study investigating sub-anesthetic ketamine at doses comparable to the antidepressant dose found that, in cocaine-dependent nontreatment-seeking volunteers, ketamine was superior to the control condition in increasing motivation to stop use and decreasing cue-induced craving (Dakwar et al. 2014). These findings suggest that the potent prefrontal effects of sub-anesthetic ketamine may serve to target addiction-related deficits that have eluded other glutamatergic modulators. The clinical safety and efficacy of sub-anesthetic ketamine is currently being investigated in a RCT (NCT01535937).

42.5 Conclusion

In the United States, classical hallucinogens are classified as Schedule I; this classification is reserved for substances of high abuse liability and with no known

medical benefit. Inasmuch as hallucinogens can be associated with substantial risks and are not established to be effective for any medical conditions, this classification is appropriate. However, the classification is problematic because it a priori dismisses agents with hallucinogenic effects as without medical benefit (ketamine being the sole exception). This has led to difficult cultural, legal, and financial obstacles being placed in the way of investigators who aim at better understanding the clinical utility, or lack thereof, of these compounds.

In light of the findings discussed above, it is not unreasonable for investigators to be interested in carefully and responsibly evaluating the efficacy of these promising but high-risk agents. Enough encouraging signals and important unanswered questions exist as to merit further clinical and mechanism-oriented research. Yet, it is exceedingly difficult at present to marshal the requisite financial and institutional resources to conduct appropriate clinical investigations (particularly with Schedule I substances such as LSD or psilocybin) to determine anti-addiction efficacy. Financial and cultural restrictions thereby continue to undermine the ability of researchers to appropriately investigate efficacy, while the lack of research establishing efficacy serves to reinforce those very restrictions. Thus the pursuit of science is stymied.

Governmental agencies or industry may be unwilling to fund such studies for cultural and political reasons, but research has managed to resume over the past decade, albeit at a much slower pace than in the 1950s and 1960s. Modern clinical research with Schedule I hallucinogens, such as psilocybin, MDMA, or ayahuasca (DMT), has been largely funded by foundations, such as Heffter, Beckley, and the Multidisciplinary Association for Psychedelic Studies (MAPS), that aim to sidestep some of the restrictions mentioned above by soliciting funds from private donors. In this way, clinical research with hallucinogens has received some modest financial support in the absence of conventional funding, and small pilot studies for nicotine and alcohol dependence are currently approaching completion at two independent academic centers. But in the absence of the millions of dollars necessary to effectively conduct large-scale RCTs, these foundations are ill equipped to bear the financial burden on their own. It may be that governmental or industry funding may be ultimately necessary to adequately assess the clinical utility of these compounds. It is unlikely, in the absence of a political sea change, that these types of funding will be available to fund clinical research for a compound already criminalized; instead, government or industry may be most likely to fund compounds under development or in preclinical investigation, as is the case with 18-MC.

42.5.1 Medicine, or Drugs of Abuse?

A question related to classification is whether hallucinogens should be designated as "medicines" or "drugs of abuse." These compounds are undoubtedly *drugs of abuse* insofar as they carry a high risk for problematic use and serious adverse consequences. These risks, as discussed earlier, are most probable when hallucinogens are used irresponsibly, by unprepared or unsuitable individuals, and in settings

without appropriate levels of support or guidance. Any investigative approach that does not adequately consider these dangers or makes light of them would be irresponsible. But does it follow that because hallucinogens might be used as drugs of abuse, they cannot possibly be medicines?

This chain of reasoning is shown to be based on a false dichotomy when one considers other high-risk medical treatments. It is difficult to find in the history of medicine another intervention where risks associated with nonmedical applications have been interpreted to indicate a lack of utility in clinical settings. The aim in clinical research is to investigate interventions in appropriate *medical* settings: a surgical procedure is tested in the operating room, for example, and pharmacotherapy in the clinic. To classify hallucinogens as Schedule I based primarily on risks emerging in nonmedical settings is tantamount to outlawing an experimental surgical procedure because it is associated with high morbidity and mortality when attempted at home with crude implements. Whatever the intervention might be and no matter how preliminary the clinical research, risks emerging from its nonmedical uses should not be given undue emphasis when drawing conclusions about medical utility in appropriate contexts. This is especially the case for intervention where a proper medical setting is crucial, as with hallucinogens. From a clinical research perspective, it is therefore appropriate to tentatively group hallucinogens alongside other high-risk interventions, such as surgery, opioids, or anesthetic agents, which necessitate various precautions, well-delineated treatment contexts, and careful screening procedures so as to minimize risk and optimize therapeutic efficacy. Whether hallucinogens ultimately take a place next to such effective but high-risk interventions remains to be determined by the appropriate research.

With a binary conceptualization of these compounds as drugs of abuse *or* medicines clearly inadequate, it is reasonable to suppose instead that hallucinogens are drugs *and possibly* medicines. This allows for an appreciation of their risks and complexities, as well as for recognition that scientific inquiry into their efficacy is promising but incomplete. While the current schedule does not brook such nuances, particularly when substances of known risk are concerned, this conceptualization can help investigators frame their research approach, especially when it comes to determining set/setting and testing procedures. Further, it may assist in transforming entrenched political and cultural attitudes towards these compounds.

The most pressing question is ultimately an empirical and straightforward one: Do hallucinogens have a role in the treatment of substance use disorders or not? As discussed above, this is a question that builds on decades of research and that addresses important gaps in our understanding. Further, it is a question that deserves to be answered, having been left unresolved for nearly half a century. Addiction is too severe a disorder, and too often resistant to available treatments, for the continued neglect of these promising compounds to be justified. We have come to realize that hallucinogens can be abused as drugs; perhaps, it is time to determine whether they can be used as medicines as well.

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Addiction Treatment with Acupuncture

43

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Contents

Abstract

The National Acupuncture Detoxification Association auricular acupuncture protocol is used around the world to help people deal with and recover from substance abuse. The NADA protocol has been shown in a variety of clinical settings to be beneficial in the process of detoxification from substance abuse as well as to help with the emotional, physical, and psychological attributes involved in addictions. The NADA protocol has been effective in a wide range of addictive disorders that include opiates, alcohol, cocaine, cannabis, methamphetamine, and benzodiazepines. Clinical reports have indicated that the NADA protocol has been effective for dually diagnosed patients. Patients report a decrease in anxiety and depression and a reduction in violence, improvement in compliance with medication protocols, and reduction of adverse reactions to psychotropic medications. Since the beginning of the new millennium, in the age of evidenced-based medicine, the use of this modality has increased significantly worldwide, despite the lack of a large amount of randomized controlled trials indicating its efficacy.

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43.1 Introduction

Acupuncture is a modality of treatment practiced in China for the past 2,500 years. In 1972, Dr. H. L. Wen, a neurosurgeon from Hong Kong, discovered that one of his patients reported reduced withdrawals and cravings for opiates following auricular acupuncture utilized for analgesia. Dr. Wen and Dr. Cheung published their results of treating 40 heroin and opium addicts with electropotentiated ear acupuncture in the Asian Journal of Medicine.

The following year Dr. Michael Smith, medical Director of the Lincoln Hospital Detox Program, began using acupuncture as an adjunct treatment for their patients, following a 10-day methadone detoxification cycle. Clients reported less malaise, feeling more relaxed, and a reduction of opiate withdrawal symptoms. It was accidentally discovered that simple manual needling produced a more prolonged effect compared to electric stimulation. In 1978, the clinic discontinued the use of methadone as a part of its detoxification protocol. During the crack cocaine epidemic of the 1980s, the protocol was utilized with some success to treat these patients as well.

43.2 Acupuncture Applications

43.2.1 The NADA Ear Protocol

Chinese medical theory, though scientific in its own right, is built on the foundation of ancient philosophical thought. The theory of the yin and yang is one such philosophy. The basic premise of this theory is that in nature there is constant change. Yin and yang represent two broad categories of opposite yet complementary concepts. More specifically, yin is what maintains and endures, is nourishing, and supports growth. Some examples of yin are earth, autumn, cold, and moisture. On the other hand, yang is what is creative and generating. Some examples of yang are heaven, spring and summer, heat, and dryness.

Auriculotherapy is a therapeutic modality of acupuncture in which external ear stimulation is utilized to treat health conditions in other parts of the body. The needling takes place with five thin, sterile, stainless steel needles under the surface of the skin of the outer ear. The practice of ear acupuncture is based on the fact that there is an anatomical arrangement of points on the external ear that represent an inverted homunculus. More specifically, the head is represented in the lower part of the ear, the hands and feet towards the top, and the internal organs within the depressions of the outer ear.

The NADA five points are the sympathetic, shen men (spirit gate), kidney point, liver point, and lung point. These were chosen based on Chinese medical theory and clinical indication, as well as lower electrical resistance and pain sensitivity.

They are located on the deep, dark, cavernous parts of the ear, i.e., the yin side. The combination of all five points has the result of a yin tonification, restoring the calm inner qualities akin to serenity.

The needling of the sympathetic and shen men points produces calming, relaxing, and centering effects. The kidney, liver, and lung points correspond to yin organs. The yin organs are deemed as nourishing, restorative, and supportive. In modern Western medicine, these organs are the organs of elimination in the body and, hence, relate to detoxification and cleansing.

Dr. Michael Smith at the Lincoln Recovery Center developed sleepmix tea which is used in prior to the NADA protocol. It contains three parts chamomile and one part each peppermint, yarrow, hops, skullcap, and catnip. It is believed to calm and soothe the nervous system, stimulate circulation, and eliminate waste products.

43.2.2 Research and the NADA Protocol

Dr. H. L. Wen was the first physician to report successful treatment of withdrawal symptoms with acupuncture in 1973. He initially observed an opiate addict receiving electroacupuncture for presurgical analgesia and, as a result, reported relief of withdrawal symptoms.

In 1987, Bullock studied 54 patients with alcohol dependence in an inpatient program that were randomly assigned to either the NADA treatment protocol or needling at nearby ear points (the "sham" group). The receivers of the NADA protocol treatment showed better outcomes for cravings of alcohol and subsequent relapses. These results were replicated by the same group in 1989 during which 80 patients were divided randomly in two groups, 40 in the NADA group and 40 in the "sham" group. After 8 weeks, 21 patients in the first group remained in the program compared to one in the latter group.

Washburn in 1993 reported that opiate addicts receiving the NADA treatment protocol had better program attendance than subjects receiving acupuncture on placebo sites.

Konefal in 1995 conducted a study during which 321 subjects were randomly assigned to three groups: a one-needle shen men point, the NADA protocol five-point treatment, and a NADA protocol five-point treatment plus selected body points for self-reported symptoms. All three groups showed a reduction in the percentage of positive urine drug screens, with the latter two groups showing the largest reduction.

Shwartz, Saitz, Mulvey, and Brannigan in 1999 published a retrospective cohort study of 8,000 clients discharged from detoxification programs in Boston, MA. Outpatients that received acudetox treatment had statistically significant lower rates of readmission than residential patients who did not receive acudetox treatment.

A pilot study in 2000 by Russell, Sharp, and Gilbertson of 86 subjects with a history of addiction and multiple arrests found a statistically significant increase in program retention and positive trend towards fewer arrests and fewer positive urine toxicology results of the group that received acudetox treatment compared to the group that did not.

Avants in 2000 conducted a study in which 82 cocaine-dependent methadone-maintained subjects were randomly assigned to three groups. The results found 58 % of the acudetox group versus 24 % of the sham group, and 9 % of the relaxation video group had cocaine-free urines. A large six-state nationwide study published in JAMA by Margolin et al. in 2002 found no statistically significant difference between the acudetox and control groups.

Bier et al. in 2002 studied the effect of acudetox in nicotine cessation. They found that in 1 month 10 % of receiving acudetox were not smoking compared to 22 % of those receiving sham acupuncture with education counseling and 40 % of those receiving acudetox and clinical intervention.

43.2.3 Applications and Outcomes

While originally intended for use in opioid abuse and dependence, the NADA protocol has been effective in a wide range of addictive disorders that include opiates, alcohol, cocaine, cannabis, methamphetamine, and benzodiazepines. For the most part, this form of treatment has been effective as adjunctive to standard treatment protocols.

43.2.3.1 Opiate Addiction

It has been reported from the Lincoln Recovery Center that acudetox provides nearly complete relief of observable acute opiate withdrawal symptoms in 5–30 min and lasts for 8–24 h. The duration of the effect of treatment has been subjectively reported by patients as increasing with every subsequent treatment. It has also been reported that patients that are intoxicated prior to initiating the treatment session feel less intoxicated following treatment. During treatment of acute opiate withdrawal, the NADA protocol is administered 2–3 times daily. In conjunction with methadone or buprenorphine, it is administered once daily. In addition to the above, the NADA protocol in an opiate detoxification program typically results in a 50 % increase in retention. In methadone maintenance programs that utilize this form of adjunctive treatment patients report a decrease of methadone side effects and a decrease in positive urine toxicology results (Margolin 1993).

43.2.3.2 Alcohol Addiction

Retention in alcohol detoxification programs increase up to 50 % when an acudetox component is incorporated as an adjunctive treatment. Woodhull Hospital in Brooklyn, New York, reported that 94 % of the patients in the acudetox group remained abstinent compared to 43 % of the control group.

43.2.3.3 Cocaine Addiction

Acudetox recipients report calmness and decreased craving to use cocaine as soon as following the first treatment. A study of patients enrolled in a methadone maintenance program with concurrent cocaine dependence, after receiving

8 weeks of auricular acupuncture treatments, had a 44 % abstinence rate. Overall, the subjects reported decreased craving and increased aversion to cocaine-related cues (Margolin 1993). At the Lincoln Recovery Center, 80 % of 226 patients with a history of cocaine dependence had negative toxicology results. Women in Need, a program for crack-addicted women in New York City, reported an average of 3 visits per year for patients receiving conventional outpatient treatment, 27 visits per year for acudetox with conventional treatment, and 67 visits per year for those receiving acudetox, conventional treatment, and an educational component.

43.2.3.4 Methamphetamine Addiction

The Hooper Foundation, a public detoxification program in Portland, Oregon, reported a 5 % retention of methamphetamine-addicted patients without acudetox versus a 90 % retention rate of patients that received the treatment.

43.2.3.5 Marijuana Addiction

Anecdotal reports indicate a reduction in craving and an improved subjective sense of well-being following acudetox.

43.2.4 Special Populations

Substance abuse treatment programs that treat groups such as adolescents; elderly; women; culturally defined populations; gay/lesbian/transgender patients; homeless; veterans; incarcerated patients; patients with significant medical comorbidities such as HIV/AIDS, hepatitis, and mental illness; and trauma survivors have found the NADA protocol particularly helpful. These groups have more trouble maintaining their sobriety due to added stressor of discrimination and marginalization. In pregnant women, acudetox has been an effective alternative to treatment especially when medication-based treatment is not indicated or available. The Lincoln Recovery Center has been treating more than 100 pregnant cocaine users per year.

Clinical reports have indicated that the NADA protocol has been effective for dually diagnosed patients. Patients report a decrease in anxiety and depression, and programs a reduction in violence, improvement in compliance with medication protocols, and reduction of adverse reactions to psychotropic medications.

43.2.5 International Perspectives

Currently, the National Acupuncture Detoxification Association protocol is utilized in 2000 drug and alcohol treatment centers in 40 countries. It is used in 130 prisons in England. This program was expanded because of an 80 % reduction in violent incidents. In New York City following the terrorist attacks on 9/11/2001 and in New Orleans following Hurricane Katrina in 2005, posttrauma treatments were given to community members, and treatments for firemen have been established in both cities. Ear acupuncture or stress has been used by thousands of military

personnel in India. In Northern Europe, 3,000 nurses have been trained in 100 different government facilities. The Drug Abuse Resistance Education (D.A.R.E.) program in Thailand has provided ear acupuncture for Burmese tribes in border camps.

In May 2008, at the Kiryandongo Refugee Settlement Camp in Uganda, 21 former healthcare worker refugees were trained in the NADA protocol to treat the Kenyan refugee population that fled their country and entered Uganda due to the postelection violence that erupted in Kenya. Over 500 refugees were treated, with improvements in mood and sleep, decreased aggression and grief, and decreased substance abuse (mostly alcohol and tobacco use), and in children a decrease in bedwetting. Within a week, the temporary camp was moved to a permanent camp where the Kenyan refugees joined Sudanese and Ugandan refugees. Acudetox treatments continued at the camp with the participation of all three national groups. The community leaders reported that issues such as domestic abuse, stress, and alcoholism were significantly reduced since the implementation of acudetox treatments. In a period of 18 months, over 29,000 acupuncture treatments were provided.

43.3 Conclusion

Auricular acupuncture is a very effective adjunctive form of addiction treatment. This is evident in the large number of anecdotal reports from both clinicians and patients that attest to its effectiveness. What makes it even more attractive as a form of treatment is its low risk of side effects and low cost. Since the beginning of the new millennium, in the age of evidenced-based medicine, the use of this modality has increased significantly worldwide, despite the lack of a large amount of randomized controlled trials indicating its efficacy.

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Transcraneal Magnetic Stimulation (TMS) as Treatment for Substance Addiction

44

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Contents

Abstract

Transcranial magnetic stimulation (TMS) is a rapidly developing noninvasive physical approach to psychiatric treatment, including substance use disorders. It involves projecting a fluctuating magnetic field (magnetic pulses), usually repetitively (rTMS), through the skull into the brain, which generates electrical currents in brain tissue and, thus, modulates neuronal firing. TMS treatment of addiction is still in an early stage and must be considered experimental. The mechanism of TMS therapeutic action in addiction is not definitively established, but may include modulation of neurotransmitter activity (especially dopamine and glutamate) in brain regions mediating addiction, such as the dorsolateral prefrontal cortex (Hayashi et al. Proc Natl Acad Sci USA 110:4422–4427, 2013), and disruption of cue-induced drug craving. Most, but not all, studies found reduced drug craving in the active TMS group vs. the sham group. TMS does appear well tolerated by individuals with addiction; there are no reported serious or unexpected adverse events. Research is being conducted to evaluate the safety and efficacy of this novel intervention.

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44.1 Introduction

Transcranial magnetic stimulation (TMS) is a rapidly developing noninvasive physical approach to psychiatric treatment which involves projecting a fluctuating magnetic field (magnetic pulses), usually repetitively (rTMS), through the skull into the brain (Kluger and Triggs 2007; Rossini and Rossi 2007). This generates electrical currents in brain tissue (via electromagnetic induction) which modulate neuronal firing. In general, low-frequency ($\leq$1 Hz) TMS inhibits neuronal activity, while higher-frequency TMS stimulates activity, although exceptions have been noted. Because of synaptic connections, there are distal effects (both cortical and subcortical, ipsilateral and contralateral) on neural activity (Bestmann et al. 2008; Denslow et al. 2005; Li et al. 2004; Paus et al. 2001), regional cerebral blood flow (Speer et al. 2003), and neurotransmitter activity (Cho and Strafella 2009). TMS can be thought of as targeting brain circuits, rather than specific brain chemicals (e.g., neurotransmitters). Because it is applied directly to the brain, it may be better tolerated than systemic medications by some patients, e.g., pregnant women, the elderly, or those with severe medical conditions such as heart disease. rTMS is being studied as treatment for a wide variety of psychiatric disorders (Fitzgerald 2011; Kammer and Spitzer 2012), including depression, schizophrenia, bipolar disorder, obsessive-compulsive disorder, post-traumatic stress disorder, and autism, and is already approved by many national regulatory authorities as treatment for major depressive disorder.

44.2 TMS Treatment of Addiction

TMS treatment of addiction is still in an early stage and must be considered experimental (Bellamoli et al. 2013). There are only about a dozen human studies in the published literature, all dealing with nicotine (tobacco) (Table 44.1), cocaine (Table 44.2), or alcohol (Table 44.3) use disorders. A majority are single-session experimental laboratory studies and appear well designed (e.g., using single- or double-blind sham TMS), but only three measured actual drug use in addition to drug craving. Only two studies (both with nicotine addiction) are outpatient-controlled clinical trials, the longest of 4-week duration. All but two studies targeted TMS pulses to the dorsolateral prefrontal cortex (DLPFC), a brain region considered important in mediating addiction which is also targeted in depression treatment. All but three studies used high-frequency (5–20 Hz) rTMS, which is considered to stimulate neuronal activity.

Most, but not all, studies found reduced drug craving in the active TMS group vs. the sham group. However, there are too few studies and substantial heterogeneity in study characteristics (except for the target brain region, which is almost always the DLPFC), making it difficult to definitively identify common factors associated with a beneficial treatment response. For example, the optimal TMS characteristics (e.g., frequency, number of pulses), duration of treatment, and combination with other smoking cessation treatments (medication and

Table 44.1 Published studies of repetitive transcranial magnetic stimulation (rTMS) and nicotine craving

		TMS parameters				
Site of pulses	*N*	Pulse frequency (Hz)	# Sessions	Total # pulses	Outcome	Authors
Superior frontal gyrus	15	10	1	4,500	↑ cue-induced craving ↓ spontaneous craving	Rose et al. (2011)
Superior frontal gyrus	15	1	1	450	No Δ cue-induced craving ↑ spontaneous craving	Rose et al. (2011)
L DLPFC	14	20	2	2,000	↓ smoking No Δ spontaneous craving	Eichhammer et al. (2003)
L DLPFC	11	20	1	1,000	↓ spontaneous craving	Johann et al. (2003)
L DLPFC	48	10	10	10,000	↓ smoking ↓ cue-induced craving	Amiaz et al. (2009)
L & R DLPFC	15[a]	20	20	15,000 per side	↓ spontaneous craving first week only No Δ smoking	Wing et al. (2012)
L DLPFC	16	10	1	3,000	↓ cue-induced craving	Li et al. (2013)
L DLPFC	10	1	1	1,800	↓ cue-induced craving	Hayashi et al. (2013)

N number receiving active rTMS, *DLPFC* dorsolateral prefrontal cortex, *L* left, *R* right, *NRT* nicotine replacement therapy

[a]Comorbid schizophrenia receiving nicotine replacement therapy and weekly counseling

psychosocial) remain unknown. Thus, no particular TMS application can be recommended for addiction treatment at this time. TMS does appear well tolerated by individuals with addiction; there are no reported serious or unexpected adverse events.

The mechanism of TMS therapeutic action in addiction is not definitively established, but may include modulation of neurotransmitter activity (especially dopamine and glutamate) in brain regions mediating addiction, such as the dorsolateral prefrontal cortex (Hayashi et al. 2013), and disruption of cue-induced drug craving.

44.2.1 rTMS and Nicotine (Tobacco) Addiction

We identified five published studies using rTMS to treat nicotine addiction (Table 44.1), including two which were double-blind, sham-controlled clinical trials with nicotine-dependent outpatients (Amiaz et al. 2009; Wing et al. 2012).

Table 44.2 Studies of rTMS and cocaine craving

Site of pulses	*N*	TMS parameters: Pulse frequency (Hz)	TMS parameters: # sessions	TMS parameters: Total # pulses	Outcome	Authors
R DLPFC	6	10	1	2,000	↓ spontaneous craving	Camprodon et al. (2007)
L DLPFC	6	10	1	2,000	No Δ spontaneous craving	Camprodon et al. (2007)
L DLPFC	36	15	10	6,000	↓ spontaneous craving	Politi et al. (2008)
L DLPFC	33	5	20	25,000	↓ spontaneous craving ↓ cocaine use	Ribeiro et al. (2013) (unpublished)

N number receiving active rTMS, *DLPFC* dorsolateral prefrontal cortex, *L* left, *R* right

Table 44.3 Studies of rTMS and alcohol craving

Site of pulses	N	TMS parameters: Pulse frequency (Hz)	TMS parameters: # sessions	TMS parameters: Total # pulses	Outcome	Authors
R DLPFC	30	10	10	9,800	↓ spontaneous craving	Mishra et al. (2010)
Dorsal ACC	1	1	21	37,800	↓ spontaneous craving	De Ridder et al. (2011)
L DLPFC	10	20	10	10,000	No Δ spontaneous craving ↓ attention to alcohol cues	Hoppner et al. (2011)
R DLPFC	15	20	1	1,560	No Δ spontaneous craving	Herremans et al. (2012)
R DLPFC	29	20	1	1,560	No Δ spontaneous craving	Herremans et al. (2013)
Bilateral[a] DLPFC	3[b]	20	20	(Not stated)	↓ spontaneous craving ↓ depression	Rapinesi et al. (2013)

N number receiving active rTMS, *ACC* anterior cingulated cortex, *DLPFC* dorsolateral prefrontal cortex, *L* left, *R* right
[a]Deep (H) coil generating bilateral TMS pulses
[b]Comorbid dysthymic disorder, treated with antidepressants and anxiolytics

Both trials applied high-frequency rTMS pulses (10 or 20 Hz, respectively) to the DLPFC (either left or bilaterally) for multiple daily sessions (2 or 4 weeks). In the first trial, active rTMS (compared to sham) significantly reduced both cue-induced craving and cigarette smoking (Amiaz et al. 2009). In the second trial, involving participants with comorbid schizophrenia, active rTMS significantly reduced spontaneous craving only during the first (of four) week of treatment, with

no effect on cigarette smoking (Wing et al. 2012). Thus, the effectiveness of TMS for smoking cessation in a realistic clinical setting remains uncertain.

44.2.2 rTMS and Cocaine Addiction

We identified two published and one unpublished study using rTMS to treat cocaine addiction (Table 44.2), including one small, open-label outpatient trial (Politi et al. 2008) and one double-blind, sham-controlled outpatient clinical trial (Ribeiro et al. 2013). Both trials applied high-frequency rTMS pulses (10 or 20 Hz, respectively) to the left DLPFC for multiple daily sessions (2 or 4 weeks). Both trials reported significantly decreased spontaneous craving – developing only in the second week of treatment in the open-label trial and linearly over time in the controlled clinical trial. The controlled clinical trial also reported significantly decreased cocaine use, verified by urine drug testing (drug use wasn't reported by the open-label trial). Thus, there is limited clinical trial evidence that at least one week of high-frequency TMS applied to the left DLPFC reduces cocaine craving and use.

44.2.3 rTMS and Alcohol Addiction

We identified six published studies using rTMS to treat alcohol addiction (Table 44.3), including one single-blind, sham-controlled trial involving inpatients no longer in severe acute withdrawal (Mishra et al. 2010). That trial reported significantly decreased spontaneous craving after ten sessions of high-frequency (10 Hz) rTMS applied to the right DLPFC.

44.3 Conclusion

High-frequency (5–10 Hz) rTMS applied to the DLPFC is a noninvasive physical approach to addiction treatment that has seen limited evaluation in controlled clinical trials for nicotine, cocaine, and alcohol addiction and is not approved for this indication by any national regulatory authority. Two outpatient-controlled clinical trials in nicotine addiction gave conflicting results, with the negative trial involving outpatients with comorbid schizophrenia. Two outpatient clinical trials (one open-label) in cocaine addiction both found decreased craving, with the controlled trial (unpublished) also reporting decreased cocaine use. One inpatient controlled clinical trial in alcohol addiction reported decreased craving. In summary, the clinical trial evidence supporting rTMS as treatment for addiction is very limited. Therefore, while rTMS is well tolerated, it cannot be recommended at this time as a first-line treatment for addiction.

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Nutrients, Phytomedicines, and Mind-Body Treatments for Substance Abuse

45

Richard P. Brown and Patricia L. Gerbarg

Contents

Abstract

Substance abuse programs continue to search for nonpharmacological treatments to assist patients during withdrawal and for relapse prevention. The craving, dysphoria, insomnia, and discomfort that drive addictions cannot be adequately treated with pharmacological agents which may be addictive or contraindicated due to comorbid conditions. The treatment of addictions is often complicated by physical pain; poor nutrition; emotional disorders such as depression, anxiety disorders, and posttraumatic stress disorder; and medical problems such as traumatic brain injury, neurological deterioration, lung disease, liver disease, and HIV. Nutrients, herbs, and mind-body practices that ameliorate physical and psychological aspects of addiction as well as its medical complications are gaining acceptance commensurate with their growing evidence base.

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45.1 Introduction

Nutrients, including vitamins, minerals, omega-3 fatty acids, and metabolites, can be beneficial in the treatment of substance abuse and its many comorbidities. Among the advantages of using nutrients, herbs, and mind-body practices are the following: little or no risk for dependence or withdrawal symptoms; fewer and less severe side effects than most prescription drugs; beneficial effects on comorbid conditions; and less risk of exacerbating abuse-related disorders such as alcoholic cirrhosis, hepatitis, or HIV. Furthermore, vitamins and nootropics (cognitive enhancers) may improve brain functions that have been compromised by substance abuse, poor nutrition, and traumatic brain injuries. Nutrients also have a role in the prevention and treatment of fetal alcohol syndrome. Dysphoria, anxiety, depression, and anger are major factors that contribute to substance abuse. Certain mind-body practices can rapidly reduce the effects of such negative emotions, improve emotion regulation, and provide new tools for dealing with stress.

This chapter focuses on treatments supported by an evidence base and by plausible physiological mechanisms of action. The relatively small scale of research on many natural treatments reflects the imbalance of funding and the difficulty of patenting natural products. In contrast, patentable, synthetic pharmaceuticals can be sold at a large profit to offset the costs of high-quality research. Taking into consideration that the playing field for research is far from level and that nutrients, herbs, and mind-body treatments tend to have fewer side effects, the evidential threshold for trying natural treatments could be lowered, particularly for patients who do not respond well or who are unable to tolerate standard treatments.

The same principles used in treatment with prescription medications apply to the use of nutrients and phytomedicines. Documentation of physician-patient discussion of risks, benefits, and the pros and cons of both standard and alternative approaches is advisable (Brown et al. 2009). The risk of adverse effects can be minimized by starting with lower doses in patients who are elderly, frail, or sensitive to medications and monitoring for side effects while increasing doses over a period of days to weeks, depending on tolerance. Herbs and nutrients can be strategically combined for synergistic effects.

45.2 Nutrients, Phytomedicines, and Mind-Body Treatments

45.2.1 Nutrients

Vitamins, minerals, fatty acids, amino acids, and metabolites have been shown to be beneficial in all phases of substance abuse treatment. In addition to reducing craving and relapse, many supplements prevent or ameliorate adverse effects of drinking on the liver, brain, and other organ systems. Vitamin B12 and folate are important for the antidepressant effects of *S*-adenosylmethionine (SAMe) and prescription medications (see below). Vitamin B6 is essential for SAMe hepatoprotection.

45.2.1.1 Vitamin B1 (Thiamine)

Vitamin B1 (thiamine) supplementation has become a standard complementary treatment for neurological sequelae, including Korsakoff psychosis, polyneuropathy, and myopathy, associated with thiamine deficiency in chronic alcohol abusers. In therapeutic doses, B vitamins rarely cause adverse reactions. A combination of B6 and B12 vitamins and folate reduces homocysteine levels (elevated homocysteine correlates with increased risk of cardiovascular disease) but may slightly increase the risk of restenosis of cardiac stents in men only whose baseline homocysteine level is less than 15 μmol/l (Lange et al. 2004).

45.2.1.2 Magnesium

Acute alcohol administration can cause sudden severe vasoconstriction and decreased cerebral blood flow. Alcohol use, particularly "binge drinking," is associated with headaches, strokes, sudden death, and worse outcomes in patients with brain injury. Low levels of intracellular and extracellular magnesium modulate a cascade of events involved in cerebrovascular constriction. In animal studies, magnesium infusion attenuated alcohol-induced vasoconstriction. In humans, intravenous magnesium sulfate relieved alcohol-associated headaches (Altura and Altura 1999; Barbour et al. 2002).

In a 12-week randomized controlled trial (RCT), magnesium-l-aspartate 723 mg/day given to heroin addicts undergoing treatment with methadone decreased the percentage of positive urinary tests and the rate of relapse to heroin use during methadone maintenance. Preclinical in vitro and animal studies point to a role for Mg^{2+} in reducing the intensity of dependence on nicotine, cocaine, amphetamine, ethanol, and other drugs. Magnesium has moderate stimulative effects on the reward system and reinforcement without causing dependence (Nechifor 2008). It is thought to reduce caffeine and nicotine dependence by release of dopamine and glutamate. A 4-week RCT found that magnesium enabled heavy smokers to reduce the number of cigarettes smoked per day (Nechifor et al. 2004). Cocaine-dependent patients given mg-L-aspartate 732 mg/day in a 12-week RCT showed decreased cocaine craving and cocaine use (Margolin et al. 2003).

45.2.1.3 Taurine and Acamprosate

Taurine, an amino acid and antioxidant, prevented toxic damage to the liver during alcohol withdrawal in rats by reducing acetaldehyde levels (Watanabe et al. 1985). Supplementation with taurine 1–4 gm/day reduced alcohol withdrawal symptoms better than placebo in an RCT study of 60 patients (Ikeda 1977). Taurine has also been used to reduce alcohol craving. Acamprosate, a medication derived from taurine, is more effective than taurine for reducing alcohol craving in clinical practice. For this reason and because medical insurance will cover the cost of acamprosate, few patients will require taurine.

45.2.1.4 Acetyl-L-Carnitine (ALCAR)

Alcohol abuse is associated with low serum carnitine levels. Abstinent alcoholics treated with acetyl-L-carnitine (ALCAR) 2,000 mg/day for 3 months showed better

performance on neuropsychological testing than control subjects (Tempesta et al. 1990). Several rat studies have shown that ALCAR protects against alcohol-induced metabolic abnormalities, including glutathione (major antioxidant) depletion (Calabrese et al. 2000, 2002). Acetyl-L-carnitine may have a role in the prevention and treatment of cognitive deficits associated with alcohol abuse. One rodent study found that ALCAR protected against tremor during alcohol withdrawal and reduced alcohol consumption (Mangano et al. 2000).

45.2.1.5 *N*-Acetylcysteine

Animal studies have indicated that *N*-acetylcysteine (NAC) inhibits cocaine-seeking behavior. In a double-blind randomized placebo-controlled (DBRPC) cross-over trial, 15 hospitalized nontreatment-seeking patients with cocaine dependence were given four doses of either NAC (600 mg) or placebo. In rating their responses to watching slides depicting cocaine and cocaine use, subjects reported less interest and less desire to use cocaine while they were taking NAC. This study suggests that NAC may reduce cocaine cue reactivity (LaRowe et al. 2007).

A 4-week open pilot study in 23 treatment-seeking cocaine-dependent patients tested NAC in doses of 1,200 mg/day, 2,400 mg/day, or 3,600 mg/day. The two higher doses of NAC were associated with better retention rates. A majority of the 16 subjects who completed the study either terminated use of cocaine completely or significantly reduced their use of cocaine during NAC treatment. All three doses were well tolerated. These findings support the value of further trials of NAC as an adjunct for treating individuals with cocaine dependence (Mardikian et al. 2007).

Reducing marijuana use may be more appealing to young adults than giving it up completely, as demonstrated in a pilot trial of NAC. Men (n=18) and women ($N = 6$) ages 18–21 years, who wanted to reduce marijuana smoking, but not stop it entirely, took NAC 1,200 mg b.i.d. for 4 weeks. The subjects reported significant reductions in three out of four domains on the Marijuana Craving Questionnaire. Semiquantitative urine cannabinoid levels did not change (Gray et al. 2010). In an 8-week DBRPC study of 15–21-year-old marijuana users, the treatment group received NAC 1,200 mg/day with a contingency management intervention and brief weekly cessation counseling. During treatment participants receiving NAC had more than twice the odds of having negative urine cannabinoid tests compared to the placebo group (odds ratio = 2.4, 95 % CI = 1.1–5.2) (Gray et al. 2012).

45.2.1.6 Omega-3 Fatty Acids from Fish Oils

Ethanol (alcohol) reduces n-3 PUFAs (polyunsaturated fatty acids) in nerve cell membranes and depletes the liver of these essential fatty acids. Low n-3 PUFA levels have been associated with anxiety, depression, and cognitive dysfunction. In a DBRPC 3-month study of substance abusers with anxiety, 13 patients were given 3,000 mg/day of fish oils versus 11 patients given placebo. Those taking capsules containing 3 g of n-3 PUFAS (eicosapentaenoic acid + docosahexaenoic acid) showed a significant progressive decrease in anxiety compared to those given placebo ($p = 0.01$). The decrease in anxiety scores remained significantly lower in the n-3 PUFA treatment group versus placebo at 3- and 6-month follow-ups

(Buydens-Branchey and Branchey 2006). Considering the known health benefits of omega-3 fatty acids, one could recommend their use while waiting for further studies to validate these encouraging results.

45.2.1.7 *S*-Adenosylmethionine

S-adenosylmethionine (SAMe) has significant potential as a valuable treatment for all stages of alcoholism because it has both antidepressant and hepatoprotective effects. Many alcoholics suffer from depression. SAMe is as effective as prescription antidepressants, but it has fewer side effects. Unlike prescription drugs, it does not burden liver metabolic systems and does not cause liver enzyme elevations (a common side effect of SSRI's). SAMe has been shown to improve liver function and to reduce alcohol-induced liver toxicity through several mechanisms. First, SAMe reduces serum alcohol levels, but does not increase serum acetaldehyde levels. Second, SAMe protects liver mitochondria from damage by alcohol (Lieber 2002). Third, SAMe maintains supplies of the body's primary antioxidant, glutathione. The US Department of Health and Human Services Research and Quality Assessment report (AHRQ 2007) concluded that SAMe was as effective as prescription antidepressants but with fewer side effects and that it improved indicators of hepatic dysfunction (for reviews of SAMe, see Brown et al. 2002; Bottiglieri 2002, 2013).

SAMe, Folate, and B12: Metabolic Pathways

S-adenosylmethionine (SAMe) is produced primarily in the liver and secondarily in the brain by the condensation of methionine and adenosyl triphosphate (ATP), catalyzed by the enzyme methionine methyltransferase (MAT). Methyltransferase enzymes catalyze methylation, the process in which SAMe avidly donates methyl groups to DNA bases, proteins, phospholipids, neurotransmitters (serotonin, norepinephrine, and dopamine), and many other cellular components. It also donates sulfate groups, for example, in the synthesis of glutathione, the primary endogenous antioxidant. Methylation controls gene expression, turning "on" or "off" transcription of proteins; posttranslation modifications of proteins that affect enzyme activity; the ability of phospholipids to maintain cell membrane integrity; and the functioning of receptors in the lipid membrane bilayer (Bottiglieri 2013).

Methylation by SAMe for production of major neurotransmitters involved in mood regulation requires cofactors B_{12} (methylcobalamin) and folate. Low levels of these cofactors are associated with severe depression. The antidepressant effect of SAMe and other antidepressant medications is often enhanced by adding 1,000 mcg/day B_{12}, 800–1,000 mcg/day folate, and 50–100 mg/day B_6.

Effects of Alcohol on Hepatic Functions and Levels of SAMe and Glutathione

- Decreased SAMe content has been found in liver biopsies from cirrhotic patients.
- Hepatic SAMe deficiency is the result of the loss of MAT activity.
- Ethanol (alcohol) consumption decreases SAMe synthesis, intracellular SAMe levels, and the enzymatic activity of MAT II (Halsted 2013; Halsted and Medici 2012).

- SAMe blocks CYP2E1 effects on alcohol oxidation and the associated increase in reactive oxygen species (ROS).
- SAMe prevents alcohol upregulation of Toll-like receptor (TLR) signaling pathways that mediate proinflammatory response, fibrogenesis, and carcinogenesis in alcoholic liver disease (ALD) and other chronic liver diseases in animal models (Oliva et al. 2011).

The mechanisms of SAMe hepatoprotection against injury by alcohol and CYP2E1 have been reviewed (Cederbaum 2010). Dehydrogenase oxidizes most of the alcohol that is ingested, but at elevated ethanol concentrations and with chronic consumption, CYP2E1 has a greater role in oxidizing ethanol and generates acetaldehyde and hepatotoxic ROS. SAMe is a reversible, noncompetitive inhibitor of the catalytic effect of CYP2E1 on ethanol oxidation. Thus, SAMe blocks CYP2E1 oxidation of alcohol, reducing production of ROS that damage mitochondria and membranes.

Chronic alcohol consumption by baboons for 18–36 months significantly depleted hepatic SAMe and glutathione and increased circulating levels of the mitochondrial enzyme glutamic dehydrogenase. SAMe attenuated the ethanol-induced increase in plasma glutamic dehydrogenase and was associated with a decrease in the number of giant mitochondria (Lieber et al. 1990).

In a 30-day DBRPC study of 64 subjects with at least a 6-year history of alcohol abuse, those given SAMe 200 mg IM/day (equivalent to 400 mg p.o.) showed significant improvements in anxiety, depression, liver function tests, fatigue, anorexia, insomnia, nausea/vomiting, treatment compliance, and abstinence compared to placebo. The group given SAMe had lower gamma-GT levels and lower serum alcohol levels compared to no change in the placebo group (Cibin et al. 1988).

A review of 17 clinical studies (Osman et al. 1993) found that SAMe improved biochemical markers (e.g., serum bilirubin, liver enzymes, cysteine, taurine, and hepatic glutathione) and symptoms (e.g., pruritus, fatigue, and jaundice) of liver disease regardless of etiology (alcoholic, nonalcoholic, infectious hepatitis, cirrhosis, cholestasis, metabolic disorders, and hepatotoxicities).

Mato and colleagues (Mato et al. 1999) conducted a 2-year DBRPC study of 123 patients with alcohol-induced liver cirrhosis reporting that patients with Child-Pugh class A or B given oral pharmaceutical-grade SAMe (AdoMet) 1,200 mg/day for at least 1 year had a mortality/liver transplantation rate of 12 % versus 29 % ($p = 0.025$) in the placebo group. At 2-year follow-up, the SAMe group continued to have lower mortality/liver transplantation rates ($p = 0.046$). In Child-Pugh C, the more severe cases, there was a trend toward reduced mortality/liver transplantation that did not reach significance. These results indicate that long-term treatment with SAMe may improve survival or delay liver transplantation in patients with alcoholic liver cirrhosis, especially in those with less advanced liver disease.

In contrast, a 24-week DBRPC study of SAMe treatment in 37 outpatients with alcoholic liver disease (ALD) included baseline liver biopsies in 24 subjects. The group given 400 mg t.i.d. of SAMe (SD4 by Abbot Laboratories) found SAMe to be no more effective than placebo in reducing liver function tests (LFTs) or fibrosis on

liver biopsy (Medici et al. 2011). The authors acknowledged that the absence of SAMe effects observed in this study may be due in part to the following limitations. The small number of completers, 13 in each group, was marginally adequate to detect meaningful effects. The number of posttreatment biopsies was even smaller (n=14). Although an attempt was made to exclude patients with severe ALD, the biopsies showed a high level of fibrosis. The authors noted that this would result in a smaller number of potentially responsive hepatocytes. Therefore, the effectiveness of SAMe would depend upon its transport, retention, and metabolism by damaged hepatocytes. Furthermore, glutathione production requires vitamin B6. The ALD subjects had subnormal B6 levels throughout the study which were not corrected. Moreover, sobriety was not guaranteed in outpatients. Subjects admitted relapse to drinking, and those whose drinking exceeded the protocol limit were dropped from the study. The reported alcohol abuse and the possibility of unreported drinking would reduce the effectiveness of SAMe and the validity of the findings. Finally, the short duration of this study, 24 weeks, may not have allowed sufficient time for SAMe benefits in patients with fibrosis of ALD. The study by Mato and colleagues (Mato et al. 1999) reported significant results after 1 year of SAMe treatment for alcoholic liver cirrhosis.

A review of 8 RCTs of ALD did not find sufficient evidence to support or refute treatment with SAMe (Rambaldi and Gluud 2006). Overall, the evidence suggests that SAMe is beneficial to liver function and repair but that in more severe cases, it requires augmentation for effectiveness. One of the weaknesses of research is the predominance of single-agent trials even when it is known that essential cofactors are deficient, for example, low B6 levels. Liver protection and repair require the rehabilitation of multiple metabolic pathways and cellular structures. Expecting a robust response to SAMe monotherapy in patients with serious ALD may be unrealistic. Further SAMe research on hepatic diseases should include more complex regimens (see below). Current treatments for ALD are quite limited, and the morbidity, mortality, and costs of hepatic disease are high. In this context, clinicians can offer patients with ALD low-risk treatments that will improve their chances for recovery by using higher doses of SAMe as the treatment foundation. The benefits of SAMe can be augmented with vitamin B6 and the nutrients and herbs discussed below.

Augmenting SAMe for the Treatment of Substance Abuse and Hepatic Dysfunction Using Dilinoleoylphosphatidylcholine, B6, and Bupleurum

Dilinoleoylphosphatidylcholine (PLPC), a polyunsaturated phospholipid, is the active antioxidant constituent of polyenylphosphatidylcholine (PPC). PLPC attenuates early effects of alcohol toxicity, partly by reducing mitochondrial injury. These benefits at the initial stages of alcoholic liver injury may prevent or delay progression to more severe forms of ALD. In alcohol-fed rats, chronic administration of a soybean-derived PLPC prevented development of cirrhosis, ethanol-induced fatty liver, and hyperlipidemia (Navder et al. 1997). Also, PLPC prevented alcohol-induced fibrosis in baboons and opposed the associated oxidative stress. Studies showed that the combination of SAMe with dilinoleoylphosphatidylcholine (PLPC)

had antifibrinogenic effects in hepatic stellate cells, effects that could be explained by the inhibition of collagen-producing mRNA and other mechanisms. In addition, SAMe blocked the generation of H_2O_2 (free radical) and restored the reduced glutathione (GSH) levels (Cao et al. 2006).

To date, no clinical trials of SAMe with PLPC augmentation have been published. In clinical practice, one of the authors (RB) finds that the addition of PLPC and Chinese herbal combinations containing Bupleurum (see below) to higher doses of SAMe (1,200–2,400 mg/day) substantially increases the benefits of SAMe in the treatment of patients with mild to severe alcohol-induced liver disease. Correction of subnormal B6 levels is also important. In future studies of patients with alcohol-related hepatic dysfunction, including fibrosis, it would be worthwhile to supplement SAMe with PLPC, B6, and Bupleurum-containing preparations.

45.2.1.8 SAMe Treatment During Pregnancy

Treating women for substance abuse-related problems during pregnancy is a challenging problem. Depression, cholestasis of pregnancy, hepatitis, and other hepatic dysfunctions are not uncommon among substance abusers. SAMe has been the standard treatment for cholestasis of pregnancy in Italy for over 20 years. Eight studies showed SAMe to be safe and effective for relief of pruritus and for reducing elevated serum bilirubin levels associated with cholestasis of pregnancy. None of the eight clinical trials reported adverse effects on mothers or children during or after they were treated with SAMe. In an RCT of pregnant women with chronic hepatitis B and elevated liver function tests (LFTs), SAMe improved liver functions in 21 % of 18 subjects. At birth and 1-year follow-up, all of the children were physically normal (Sun et al. 2010).

SAMe in the Treatment of Methamphetamine Abuse

Methamphetamine reduces dopamine and SAMe levels contributing to damage to brain functions (Cooney et al. 1998). Improvements in depression and extrapyramidal symptoms in patients with Parkinson's disease treated with SAMe suggest that SAMe may improve dopaminergic function (Di Rocco et al. 2000; Brown et al. 2009). Dr. Richard Brown has observed anecdotally that SAMe accelerated recovery in methamphetamine addicts (without bipolar disorder). Based on preclinical data, mechanisms of action, positive effects in Parkinson's disease, the low level of risk, and the known health benefits and limited standard treatment options, SAMe could be considered as an augmentation to the treatment of methamphetamine abuse.

SAMe Effects on Depression

In European countries, SAMe has been a first-line prescription antidepressant for over 25 years. The US Food and Drug Administration (FDA) approved SAMe as an over-the-counter nutraceutical in 1998 based on its very low profile of side effects. SAMe proved to be a safe and effective treatment for major depression in 16 open trials, 13 DBRPC studies, and 19 RCTs in comparison to standard antidepressants (Brown et al. 2002). SAMe protects the liver from toxic

effects of prescription drugs and does not have adverse interactions with medications (Torta et al. 1988).

SAMe has been shown to be useful as a monotherapy and as an adjunct to other antidepressants. An open trial of SAMe (800–1,600 mg/day) augmentation to antidepressant treatment for 30 depressed patients who had failed to respond to either SRIs or venlafaxine yielded a response rate of 50 % and a remission rate of 43 % (Alpert et al. 2004). In a 6-week DBRCT of 73 serotonin reuptake inhibitor (SRI) nonresponders with major depressive disorders, adjunctive SAMe (800 mg b.i.d.) significantly improved response rates and was well tolerated (Papakostas et al. 2010). The US Agency for Healthcare Research and Quality Assurance report based on a systematic review of SAMe research found no statistically significant difference in outcomes between patients treated with SAMe compared to prescription antidepressants, but SAMe caused fewer side effects (AHRQ 2007).

In an 8-week DBRPC study of 18 schizophrenic patients, oral SAMe (800 mg/day) significantly improved depression and ameliorated aggressive symptoms (Strous et al. 2009). Oral SAMe treatment for 8 weeks also significantly reduced depressive symptoms in 20 HIV-seropositive patients with a history of drug abuse and a diagnosis of major depressive disorder (Shippy et al. 2004). The evidence for antidepressant effects of SAMe is compelling (Brown et al. 2009; Bottiglieri 2013). Considerable evidence indicates hepatoprotective effects. Although the one small recent study cited above did not corroborate hepatoprotection, this may have been due to the short term of treatment, low B6 levels, patient selection, or the lack of SAMe augmentation. At the very least, SAMe does no harm to the liver and, in that regard, is superior to other antidepressants. Although further studies of oral SAMe in the treatment of alcoholism are needed, the evidence base is sufficient to justify its use treating depression, anxiety, and hepatic dysfunction in alcoholics.

SAMe and Immune Function

Substance abusers are at risk for compromised immune function due to poor nutrition, self-neglect, infections from needles, lung damage from smoking, and sexual indiscretions.

SAMe is vital for the activation and proliferation of T helper CD4(+) lymphocytes. MAT II catalyzes the synthesis of SAMe from methionine and ATP. Ethanol impairs immune function by decreasing MAT II and SAMe (Hote et al. 2008). The reduction in SAMe and MAT II may have additional adverse effects on mood and cognitive function. Supplementation with oral SAMe can reverse these deficits.

Safety of SAMe and SAMe Side Effects, Risks, and Benefits

Compared to prescription antidepressants, SAMe has a low side effect profile. It does not cause any weight gain or sexual dysfunction. The most common side effects of SAMe are nausea and loose bowels, which usually do not require discontinuation. Less common are vomiting, abdominal discomfort, overactivation, and rarely anxiety, agitation, or insomnia. As with most antidepressants, the induction of manic symptoms is a serious risk. SAMe is the only antidepressant demonstrated to be safe in patients concurrently taking MAO inhibitors (n=60) and

in alcoholics taking antidepressants or anticonvulsants (n=18). Not only were there no adverse reactions, but SAMe also reversed or prevented liver toxicity and normalized elevated gamma-glutamyl transpeptidase (GGT) in all patients taking MAOIs, anticonvulsants, or antidepressants (Torta et al. 1988).

SAMe Product Quality

Each SAMe tablet must be kept in an individual blister pack to prevent the rapid oxidation from exposure to air that would occur in bottled products. In addition, tablets must be carefully manufactured and enterically coated to delay metabolism by digestive enzymes. Inactive SAMe isomers have been found in bargain brands marketed on the web. Therefore, it is strongly recommended that patients use only pharmaceutical-grade SAMe in products that have been tested for efficacy and shelf life (effects of time on potency) (Brown et al. 2009).

45.2.2 Herbal Medicines

Phytomedicines have been used widely in the treatment of substance abuse to reduce craving, withdrawal symptoms, and hepatotoxic effects. Traditional use, animal studies, and clinical trials of mixed quality support the use of certain herbals and indicate a need for rigorous controlled trials to explore their potential efficacy. This section will focus on clinically useful herbal medicines with adequate levels of evidence for mechanisms of action, efficacy, and safety.

The following herbs reduced alcohol intake by rats bred to prefer alcohol but require more study in humans: Hypericum perferatum (St. John's Wort), *Salvia miltiorrhiza* (Red sage, Chinese sage), *Galanthus nivalis* (snow drop), *Trigonella* foenum-graecum (fenugreek).

Tabernanthe iboga (ibogaine) (see ▶ Chap. 42, "Evaluating the Therapeutic Utility of Hallucinogens for Substance Use Disorders"), *Hovenia dulcis* (raisin tree), and Asian, Chinese, and Ayurvedic herbal compounds. Although St. John's Wort (SJW) reduced alcohol craving in animal studies and has antidepressant effects, it can interfere with the metabolism of many drugs. Also SJW can cause photosensitivity and, at higher doses, side effects similar to sertraline. For a review that includes herbs supported only by preclinical studies or those that have potentially severe adverse effects, see Tomczyk et al. (2012).

45.2.2.1 Passionflower (*Passiflora incarnata*) and Lemon Balm (*Melissa officinalis*)

Passionflower extract was found to reduce tolerance and dependence on morphine, alcohol, diazepam, and delta-tetrahydrocannabinol in mouse studies (Dhawan et al. 2003). A DBRPC study of 65 opioid-dependent patients comparing clonidine augmented with passionflower versus clonidine plus placebo showed no difference in effects on withdrawal symptoms. Passionflower significantly accelerated the clonidine effects and reduced psychological symptoms of withdrawal (Akhondzadeh et al. 2001). Side effects are generally minimal at therapeutic doses but may include dizziness, confusion, ataxia, sedation, or prolonged QT intervals.

45.2.2.2 Kudzu (*Pueraria lobata*)

Kudzu root extract, containing active ingredients, diadzin, daidzein, and puerparin, was shown to reduce alcohol intake by rodents. In a small 1-month DBRPC study in veterans with alcoholism, kudzu showed no significantly greater effects on craving or sobriety compared to placebo (Shebek and Rindone 2000). In another DBRPC trial involving heavy drinkers, those taking kudzu significantly reduced the number of beers consumed and the volume of each sip (Lukas et al. 2005). Minimal side effects have been reported in studies of kudzu.

45.2.2.3 Herbs to Augment SAMe for the Prevention and Treatment of Hepatic Dysfunction

Bupleurum kaoi, *Bupleurum Chinense* (*Synonym Bupleurum Falcatum*), and *Bupleurum scorzonerifolfium*

In Asia, *Bupleurum kaoi* is widely used, often in multi-herbal products to treat liver diseases. Preclinical studies have demonstrated hepatoprotection against dimethylnitrosamine (DMN-induced fibrosis in rats). Various fractions of Bupleurum extracts demonstrated anti-inflammatory and antifibrotic action followed by increased glutathione production with antioxidant effects and decreased malondialdehyde (MDA), enhanced liver cell regeneration, and markedly increased interferon gamma. Hepatoprotective effects were higher in *Bupleurum kaoi* grown in Taiwan than in *Bupleurum chinense* from China (Yen et al. 2005). A combination of *Scutellaria baicalensis* and *Bupleurum scorzonerifolfium* induced interleukin-6-related signal transducer and activator of transcription 3 (STAT3) in rat liver after partial hepatectomy (Lee et al. 2011). Further studies are needed to determine whether these findings prove relevant to the regeneration of hepatocytes in humans.

In clinical practice, the authors (RB and PG) have found that multi-herbal preparations, Ease-2 and Ease Plus (Crane Herb) containing Bupleurum, reduce elevated LFTs in patients with mild liver disease. In more severe cases, Ease-2 or Ease Plus can be added to SAMe and other hepatoprotective herbs and nutrients.

Milk Thistle (*Silybum marianum*)

Antioxidant, antifibrotic, and hepatoprotective effects of milk thistle have been documented in many in vitro and animal studies. However, a review of 18 RCTs in patients with alcoholic and/or hepatitis B or C liver diseases noted that in the high-quality trials, milk thistle did not improve liver-related mortality or liver histology (Rambaldi et al. 2007).

Asian Ginseng (*Panax ginseng*) and American Ginseng (*Panax quinquefolius*)

Based on animal studies, *P. ginseng* may have a potential role in reducing dependence and tolerance for cocaine, amphetamines, and morphine. In animal studies, both Asian and American ginseng reduced blood alcohol levels by decreasing gastrointestinal absorption (Tomczyk et al. 2012). Clinical studies are needed to assess the potential benefits for treatment of alcohol intoxication syndrome.

In a multicenter RCT involving 212 heroin addicts, *P. ginseng* root extract containing ginsenosides was as effective as lofexidine in reducing symptoms of

withdrawal (Ward et al. 2011). *P. quinquefolius* contains an active ingredient called pseudoginsenoside F11 (PF11). In a DBRCT in 43 heroin addicts, a formula called WeiniCom or Xian Xu Qudu Jiaonang, containing *P. quinquefolius* and kratom, relieved opioid craving more quickly than buprenorphine and reduced withdrawal symptoms (Ward et al. 2011). Side effects of these herbal preparations were low compared to lofexidine.

Kratom (*Mitragynia speciosa korth*)

Kratom (*Mitragynia speciosa korth*) produces alkaloids (mitragines) only when it grows in Southeast Asia. Traditionally it has been used to treat opium withdrawal, cough, diarrhea, and musculoskeletal pain and to attain euphoria in higher doses. Mitragines bind to opium receptors. In animal studies, kratom led to tachyphylaxis and cross-tolerance with morphine. Kratom use was associated with tonic-clonic seizure in two cases, and long-term users have experienced anorexia, weight loss, constipation, and facial hyperpigmentation (Ward et al. 2011). Kratom is used in combination with other herbs, but to date there are no human studies published. Unfortunately, it is becoming a substance of abuse and has a mild abstinence syndrome similar to that of opioids. However, kratom does not cause respiratory depression and has fewer serious side effects than methadone. In areas where methadone maintenance programs are not readily available, such as in Asia, kratom may be a reasonable alternative that is less expensive and more culturally acceptable.

Mentat

Mentat is a traditional Ayurvedic formula containing ashwagandha (*Withania somnifera*), Bacopa (*Bacopa monnieri*), gotu kola (*Centella asiatica*), Indian Valerian (*Valeriana jatamansi*), Triphala churna, and other medicinal herbs. One small open series suggested it reduced relapse in abstinent alcoholics (Trivedi 1999). In animal studies, ashwagandha decreased opiate withdrawal symptoms (Kulkarni and Ninan 1997).

45.2.3 Mind-Body Practices in the Treatment of Substance Abuse

The desire to avoid or escape from negative thoughts, feelings, and painful sensations is a key factor in substance abuse and relapse. Difficulty regulating affects such as anxiety, fear, and anger is a common finding in substance abusers. Mind-body practices which are known to improve affect tolerance and affect regulation have the potential to help patients deal with difficult emotions without resorting to substance abuse. The treatment of addictions is often complicated by physical pain; emotional problems such as depression, anxiety disorders, and posttraumatic stress disorder; and medical conditions such as traumatic brain injury, neurological deterioration, lung disease, liver disease, and HIV. Studies indicate benefits of mind-body practices in recovery from substance abuse, anxiety, depression, physical injuries, and pain syndromes. Key neurophysiological mechanisms that underlie addictions are targeted by therapeutic mind-body practices.

Compounding the problem, chronic substance abuse compromises areas of the brain involved in affect regulation, attention, inhibitory control, and the ability to observe and moderate responses to intense emotions. Deficits in affect regulation increase vulnerability to relapse, particularly in early stages of recovery. Mind-body approaches can improve affect tolerance, affect regulation, and stress response during the withdrawal, early recovery, and maintenance phases of treatment.

In this discussion, the rubric, mind-body practices, encompasses all forms of yoga, qigong, zen, meditation, and breathing modalities. Although there are thousands of specific techniques, these practices share a few basic elements: movement, breathing, meditation, and often visualization. Traditional psychoanalysis, psychotherapy, and cognitive therapies support the observing ego and strive to reduce the judgmental activity of the archaic superego. Similarly, many Eastern practices cultivate detached nonjudgmental observation and letting go of thoughts, emotions, and sensations. During recovery, such practices may help put a distance between the impulse to take substances of abuse and the compulsion to act on the impulse. For example, dialectical behavior therapy (DBT) includes mindfulness and affect tolerance in the treatment of substance abuse (Dimeff and Linehan 2008). Following detoxification, patients continue to experience anxiety, depression, and often severe psychosocial and financial stress – conditions that promote relapse. Sedatives, anxiolytics, and some sedating antidepressants may be contraindicated due to high risks of abuse, dependence, overdose, or medical complications. Mind-body practices can be valuable, low-risk adjunctive treatments with standard rehabilitation, counseling, and self-help groups such as Alcoholics Anonymous and Narcotics Anonymous. Considering the complexity of substance abuse, a multimodal approach using compatible, synergistic treatments is likely to best serve the patient.

45.2.3.1 Neurophysiology of Mind-Body Practices and Substance Abuse

Evidence suggests that dysfunctions in higher regulatory centers, particularly the prefrontal cortex (PFC), and impaired inhibitory control are associated with substances of abuse. Mind-body practices may correct the disruptions in emotion regulatory systems and reward processing (Witkiewitz et al. 2012). Drawing from the literature on respiratory physiology, neuroanatomy, and brain imaging, Brown and Gerbarg (Brown and Gerbarg 2005) described a model for the neurophysiological effects of yoga breathing. The model was extended to include recent research on the inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), and the hypothalamic-pituitary-adrenal (HPA) axis (Streeter et al. 2012). Briefly, it is hypothesized that changes in the pattern of breathing send different interoceptive messages through vagal afferents to influence brain structures involved in emotion regulation, stress response, mood, bonding, and cognitive function. These pathways project to the amygdala, hippocampus, hypothalamus, thalamus, prefrontal cortex, insular cortex, and the anterior cingulate. Evidence was provided that slow gentle breathing, particularly at rates between four and six breaths per minute with equal inspiration and expiration (coherent or resonant breathing) for most adults,

increases parasympathetic tone (as indicated by HF-HRV), reduces sympathetic arousal, optimally balances the stress response system, increases top-down GABA inhibitory activity from higher centers (prefrontal cortex and insular cortex) to the amygdala, and thereby improves emotional and behavioral control. Increased HF-HRV is associated with enhanced self-regulation.

Low levels of heart rate variability (HRV) are associated with anxiety, depression, and nicotine dependence (Libby et al. 2012). A study of 15-h abstinent smokers (n=32) exposed to script-driven imagery of stressful and relaxing scenarios assessed the ability to resist smoking, and subsequent ad-lib smoking was related to the vagal reactivity to stress (HF-HRV). Stress and ad-lib smoking additively decreased HF-HRV and increased LF/HF (increased sympathetic and decreased parasympathetic response). Blunted stress-induced HF-HRV responses reflecting decreased vagal reactivity were associated with less time to initiate smoking and increased craving relief and reinforcement from smoking. The findings that stress-precipitated decreased vagal reactivity predicts the ability to resist smoking suggest that interventions that normalize vagal reactivity in early abstinent smokers may improve smoking cessation outcomes (Ashare et al. 2012).

Heavy alcohol use as well as alcohol dependence has been associated with dysregulation of the hypothalamic-pituitary-adrenal axis and the autonomic nervous system. Alcohol abuse may contribute to vagal neuropathy. In a study of 70 chronic alcoholics, vagal neuropathy was reversed in most of those who were able to maintain abstinence from alcohol, (Villalta et al. 1989).

Heroin users show decreased cardiac vagal activity, and methadone therapy immediately facilitates vagal regulation in patients with a recent lapse (Chang et al. 2012). Methamphetamine has been associated with decreased HRV and impaired vagal function, which may be related to cardiotoxic or neurotoxic effects of prolonged methamphetamine use (Henry et al. 2012).

Slow yoga breath practices can improve emotion regulation and increase HRV (Gerbarg 2008; Brown and Gerbarg 2009). Breathing gently at a rate between four and six breaths per minute, found in most mind-body traditions, reduces anxiety within minutes. One factor that is often overlooked is that simply putting attention on one's breath can reduce the respiratory rate. During meditation, practitioners often breathe at three to six breaths per minute. Thus, it may not be possible to separate the effects of meditation from all the effects of slow breathing. Activation of the parasympathetic system is emotionally soothing; increases GABA, serotonin, and norepinephrine; enhances mood and bonding; and reduces pain.

Pain is an important cause of substance abuse. Many people who begin using alcohol or analgesics for pain control progress to dependence and abuse. Fear of pain or of being unable to sleep generates anxiety, further exacerbating the problem. Anxiety is a major factor in the subjective experience of pain. Mind-body techniques such as hypnosis, relaxation, yoga breathing, and guided meditation that alleviate anxiety have been used to reduce pain. An additional mechanism by which yoga breathing may reduce or block pain perception is through stimulation of the vagus nerve which is involved in nociception (discrimination of painful stimuli). The vagus also affects baroreceptors which modulate pain awareness. Slow yoga

breath practices (4.5–6 breaths per minute) such as coherent breathing, ujjayi (ocean breath), and alternate nostril breathing reduce anxiety and induce a state of calm alertness (Brown and Gerbarg 2009, 2012). Preliminary neurophysiological data are consistent with improvements in attention, cognitive integration, and learning.

45.2.3.2 Qigong in the Treatment of Substance Abuse

Qigong includes movement, breathing exercises, guided imagery, concentration, and meditation. Mind-body practices that integrate body, breath, mind and spirit into oneness from a Chinese perspective are forms of qigong, whereas from an Indian perspective, they are forms of yoga. The word *qi* or *chi* meaning breath of life or vital energy is similar in meaning to the Sanskrit word, *prana*. *Gong* means "the skill to work with." The awareness of *qi* sensations in the body is a prelude learning how to guide the flow of qi as a means of physical, mental, and spiritual healing. Qigong masters develop the ability to emit energy (external *qi*) from their hands. This energy, like an electric current, is used for healing.

Qigong in the Treatment of Opiate Withdrawal

Eighty-six male heroin addicts (DSM-IIIR) admitted for mandatory treatment to the Changzhou Drug Treatment Center in the People's Republic of China were assigned in the order of their admission to one of three treatment groups. One group practiced qigong (PanGu) together 2–2.5 h/day and was treated with emitted qi for 10–15 min/day by a qigong master. The second group was detoxified with tapering doses of lofexidine, physical exercise, and group counseling. The third group received only emergency care for acute pain, diarrhea, or insomnia (diazepam or methaqualone). After 1 day, the qigong group showed significantly lower mean scores on the Chinese Standard Evaluation Scale of Withdrawal Symptoms. All groups had comparable mean Hamilton Anxiety Scores (Ham-A) at baseline. By day 5, mean Ham-A declined from 37.4 ± 7.5 to 8.2 ± 4.9 in the qigong group, from 33.5 ± 8.5 to 13.6 ± 6.4 in the lofexidine group, and from 35.0 ± 4.7 to 21.3 ± 11.4 in the nontreatment group (Li et al. 2002). Although there are methodological limitations, this study suggests that qigong practices may ameliorate anxiety and reduce withdrawal symptoms during opiate withdrawal.

Qigong in the Treatment of Cocaine Craving

Cocaine-dependent subjects ($n=101$) were randomly assigned to either real external qigong therapy (EQT) or sham EQT for four to six sessions over 2 weeks. Cue-elicited craving and depression decreased significantly in the real EQT versus the sham control (Smelson et al. 2012).

Qigong in the Treatment of Drug Addiction

A study evaluating the acceptability, feasibility, and effects of qigong on a non-Chinese population in an American residential drug addiction treatment center allowed clients to choose to participate in either a twice-daily qigong meditation (breathing, relaxation, inward attention, guided imagery, and mindfulness) or the

stress management and relaxation training (SMART) for up to 4 weeks. Two-thirds opted to participate in qigong, and 248 completed questionnaires. Treatment completion rate was higher (92 % in the qigong group versus 72 % in the SMART group). Within the qigong group, those who were better meditators reported greater reductions in craving, anxiety, and withdrawal symptoms. Compared to men, women meditators reported the greatest improvements (Chen et al. 2010). Limitations of this study included non-randomization, self-selection, difficulties assessing quality of meditation, and lack of reporting on the specific drugs of addiction.

45.2.3.3 Yoga in the Treatment of Substance Abuse

Hatha Yoga in the Treatment of Opioid Addiction

In a 6-month RCT, 61 patients treated for opioid addiction in a methadone maintenance program received either conventional weekly group psychotherapy or a weekly hatha yoga group. No significant differences were found between the two groups on psychological, sociological, and biological measures after 6 months (Shaffer et al. 1997). Most studies of mind-body practices schedule between two and five sessions per week to achieve substantive change. This study suggests that once-a-week Hatha yoga was as effective as once-a-week group psychotherapy as an adjunct to methadone maintenance. A once-weekly mind-body intervention, particularly in individuals under stress of detoxification, would be analogous to a subtherapeutic dose of a medication. It would be worthwhile to evaluate the effects of more frequent yoga sessions with standard treatment for methadone maintenance.

Hatha Yoga in the Treatment of Cigarette Craving

A three-arm RCT compared the effects of cardiovascular exercise, hatha yoga, or inactive control in 76 smokers following 1 h of nicotine abstinence; participants in both active interventions reported reduced craving to smoke, increased positive affect, and decreased negative affect compared to control (Elibero et al. 2011).

45.2.3.4 Mind-Body Practices with Emphasis on Slow Breathing

A study in 16 healthy subjects demonstrated that slow deep breathing combined with relaxation significantly increased pain thresholds and significantly reduced sympathetic arousal (Busch et al. 2012). A 24-h RCT (n=96) assigned cigarette smokers to two groups. The first group was briefly instructed on yoga breathing exercises and asked to use them when cravings occurred until the next visit (YBG). The control group was shown a video of a breathing exercise and asked to just concentrate on their breathing (VCG). All measures of cigarette craving were significantly reduced in the YBG group compared with the VCG (Shahab et al. 2012).

45.2.3.5 Mind-Body Practices with Slow and Rapid Breathing

Sudarshan Kriya Yoga in the Treatment of Alcohol Detoxification

Following detoxification, 60 hospitalized alcohol-dependent patients were randomly assigned to either Sudarshan Kriya yoga (SKY) breathing or standard

treatment (counseling and benzodiazepine for sleep). The SKY intervention was breath practices for 45 min every other day. In the SKY group mean reductions in BDI scores and cortisol levels were greater than in the standard treatment controls (Vedamurthachar et al. 2006). This study suggests that SKY may reduce anxiety and cortisol levels in recently detoxed alcoholic patients. Methodological issues limit its impact.

Sudarshan Kriya Yoga (SKY) in the Treatment of Opioid Dependence

In a 2-week RCT, community clinic patients with opioid dependence (DSM-IV) on agonist maintenance were given either standard treatment (n=14) or standard treatment plus Nav-Chetna Shivir (n=15), a 5-day course comprised of 2–3 h per day of yoga breathing (SKY), meditation, singing, and discussions about healthy living. After 2 weeks, there was no significant difference between groups on Addiction Severity Index. However, the yoga augmented group showed significant improvements in motivation and on the WHO Quality of Life Brief Scale physical, psychological, and social relationship domains compared to no significant change in the control group (Yadav et al. 2006). The short duration and small sample size limit the conclusions that can be drawn from this study.

Kundalini Yoga in the Treatment of Substance Abusers

The breathing practices emphasized in kundalini yoga include particularly rapid (high frequency) and forceful patterns of breathing. In a psychiatric hospital in Amritsar, India, a 90-day residential treatment program of voluntarily admitted substance abusers (n=10) provided three to four mandatory kundalini yoga sessions per day (yoga postures, breathing, meditation, and mantra); individual, group, and family counseling; vegetarian diets; herbs; vitamins; cleansing spices; music and dance therapies; spiritual studies and Sikh religious practices; energy medicine/spiritual healing (Sat Nam Rasayan); acupuncture; videos; lectures on yoga lifestyle; massage; and psychoeducation. Questionnaires at baseline, mid-treatment, end treatment, and 1-month follow-up showed significant improvements in impulsive and addictive behaviors, daily living, depression, anxiety, and relationship to self and others. The scores on Perceived Stress Scale did not improve significantly (Khalsa et al. 2008). The authors acknowledge the limitations of this study, particularly the small size and the effects of translators on testing. Also, the 1-month follow-up does not provide assessment of the long-term effects of this very intensive, multi-model treatment. However, in areas where populations are interested in extended residential treatments that integrate mind-body, spiritual, physical, lifestyle, and psychotherapeutic modalities, such programs may be desirable.

Religious and spiritual programs have been widely used in the treatment of substance abuse. Yoga programs have been used in substance abuse treatment in India for many years (Nespor 2005). Much of this work is published in Indian language publications or in documents from Indian religious institutions. These studies may not meet modern methodological and reporting standards. Western readers may consider such studies to be biased. While we can continue to wonder to what extent the benefits of such programs are due to their spiritual, emotional,

philosophical, or physical practices, the controlled clinical studies beginning to appear and the neurophysiological studies of yoga practices may lead us to better understand the synergistic interplay of these important components.

45.2.3.6 Meditation, Mindfulness, and Cognitive Behavioral Therapy

In their discussion of Mindfulness-Based Relapse Prevention (MBRP), Witkiewitz and colleagues (Witkiewitz et al. 2012) hypothesize that intentional awareness, nonjudgment, and acceptance of all components of experience enable clients to interrupt the stimulus response cycle of addictive reactivity and to develop alternative responses. They review findings that MBRP reduces the subjective experience of craving, reactivity to cues, and the amount and frequency of substance abuse. In an fMRI study, 47 smokers who were abstinent for 12 h viewed neutral images and images of smoking. They were trained and instructed to view the images passively or with mindful attention. Compared to passive viewing, mindful attention reduced craving in response to smoking images and reduced activity in an area of the subgenual anterior cingulate cortex that is involved in craving (Westbrook et al. 2011).

Transcendental Meditation for Substance Abuse

Most studies of transcendental meditation (TM) for the treatment of substance abuse are of limited quality. In one study college students ($n = 295$) who used cigarettes ($n = 37$), illicit drugs ($n = 60$), or alcohol ($n = 217$) were randomly assigned to 3 months of either TM or a wait list control. No significant effect of TM on abuse of these substances was found. The only effect was a reduction in the drinks per week in men, but not women (Haaga et al. 2011).

45.2.3.7 Guilt, Shame, Anger, Regret, Helplessness, Motivation, and Meaning

Mind-body-spirit programs can improve emotion regulation, reduce physical symptoms of withdrawal, and enhance motivation and compliance. Many patients in recovery report that these programs help them resolve feelings about their past, such as guilt, shame, anger, and regret. They may also discover a new purpose and meaning in life. Having repeatedly experienced overwhelming failures and helplessness, substance abusers lose hope and consequently the motivation needed for recovery. Learning simple natural methods to reduce their feelings of fear and anxiety restores a measure of control, self-efficacy, and hope. Patients with substance abuse problems are usually willing to participate in mind-body-spirit practices when given the opportunity.

45.2.4 Fetal Alcohol Syndrome

Fetal alcohol spectrum disorders (FASD) due to brain damage from prenatal alcohol exposure include children with mental retardation, hyperactivity, behavioral and sexual disorders, and abnormal craniofacial development. Neurotoxicity

from alcohol is multifactorial: oxidative damage, mitochondrial damage, activation of caspase enzymes (leading to apoptosis, cell death), and depletion of ATP and essential fatty acids (Das et al. 2006; Das 2006). Cholinergic neurons in the hippocampus and cerebellum are particularly vulnerable to injury and apoptosis. The rising rate of alcohol abuse including during pregnancy is a major public health concern in many countries.

Studies of neuroprotective compounds in pregnant animals exposed to alcohol have found prevention and reduction in adverse effects on fetal development. Compounds found to be beneficial in treating human brain injury due to stroke, trauma, or substance abuse neurological sequelae may also improve brain function in children with FASD. Choline, vitamins A and D, folate, nicotinamide (an amide of vitamin B3), omega-3 fatty acids, piracetam, Mentat, antioxidants, silymarin bioflavonoid, and the flowers of kudzu (*Pueraria thunbergiana*) administered during pregnancy or in the postnatal period prevented some adverse effects of alcohol on animal neonates (Monk et al. 2012; Ballard et al. 2012; Ieraci and Herrera 2006; Wainwright et al. 1990; Horrocks and Yeo 1999; Bhattacharya 1994; Neese et al. 2004; Thomas et al. 2004). Mentat contains 24 Indian medicinal herbs including brahmi (Bacopa) and ashwagandha. In one study, Puerariaeflos, the flower of *Pueraria thunbergiana*, prevented increased caspase-3 mRNA expression and protected human neuroblastoma cells (SK-NMC) from ethanol-induced apoptosis and (Jang et al. 2001).

The safety and neurodevelopmental benefits of appropriate doses of vitamins A and D, folate, nicotinamide, and omega-3 fatty acids have been demonstrated in humans. In light of the depletion of essential fatty acids, the presence of nutritional deficiencies in many populations, and the devastating life-long consequences of FASD, supplementation with these and additional nutrients is advised. For a review of the benefits of supplementation during pregnancy and lactation, see Morse (2012). Clinical trials of nutritional supplements for the prevention and treatment of FASD during and after pregnancy are needed. Until such studies are completed, it is possible to administer safe treatments that have shown beneficial effects on neonatal brain development and in cases of brain injury, ADHD, learning disabilities, and FASD.

Anecdotally, in a rural mental health clinic, Dr. Richard Brown has use cholinergic agents to treat adolescent and adult FASD patients for cognitive and behavioral symptoms. Damage to the hippocampus and cholinergic function are prominent features of FASD. Donepezil (Aricept) has been shown to improve cholinergic function and hippocampal gating in military veterans with traumatic brain injury (Silver et al. 2005). Disruption of cholinergic function in the hippocampus impairs auditory sensory gating, attention, and memory (Arciniegas 2003). Brown found that administration of donepezil to patients with FASD improved cognitive function and that benefits took at least 3 months as evidenced by reduction in hyperactivity, better attention and impulse control, and greater capacity to engage in vocational rehabilitation. Preadolescent children may become overstimulated by donepezil. However, the use of milder cholinergic enhancers such as centrophenoxine, huperzine A, and CDP-choline for children with FASD warrants research.

45.2.5 Integrative Approaches to the Treatment of Substance Abuse Disorders

Understanding the modes of action, the evidence base, and the high safety profile of the approaches described above will enable clinicians and researchers to judiciously integrate phytomedicines and mind-body practices with standard treatments for optimal patient outcomes. Here is a sample of an integrative plan for treatment of substance abuse.

Integrative Plan for Treatment of Substance Abuse

1. Correct nutritional imbalances: thiamine (B1), folate, B vitamin complex, and an A–Z multivitamin. Brewer's yeast in two rounded tbsps twice a day (Lewis Labs) is an inexpensive source of B vitamins and trace minerals.
2. For neuroprotection: 3,000–6,000 mg/day fish oils (omega-3 fatty acids) (eicosapentaenoic acid + docosahexaenoic), 600–800 mg/day magnesium, 1,800 mg b.i.d. *N*-acetylcysteine (NAC), and 1,000–3,000 mg/day acetyl-L-carnitine.
3. Refer to self-help support groups: Alcoholics Anonymous, Adult Children of Alcoholics, and Al-Anon.
4. Prescription medications as appropriate:
   a. Naltrexone, acamprosate, or both for alcohol dependence
   b. Topiramate 200–400 mg/day or isradipine to reduce craving for alcohol, cocaine, and other drugs
   c. Valproate for bipolar patients who abuse alcohol or marijuana
5. Evaluation for possible ADD/ADHD. In such cases, stimulants may reduce drug dependence.
6. Mind-body-spirit practices such as yoga, qigong, vipassana meditation, MBRP or mindfulness meditation with CBT, MBSR, a DBT.
7. SAMe to improve mood, liver function, immune function, for neuroprotection, and to help reduce alcohol intake. To enhance hepatoprotective effects of SAMe: B6, polyenophosphatidylcholine, betaine, and *Bupleurum*. SAMe is contraindicated in bipolar patients.
8. Formulation of the treatment plan: Discussion with the patient about the treatment options and prioritizing of the target symptoms. Documentation of this discussion in the medical record.
9. Assessment of the feasibility of doing the intervention, taking into account patient motivation, costs, and likelihood of compliance.
10. Time Frame and Treatment Phase
    a. The first 2 weeks: detoxification, physical stabilization, and engagement in treatment. Initiate nutrients, herbs, and slow breathing practices to correct nutritional deficiencies and reduce anxiety, insomnia, withdrawal symptoms, and pain. Cranial electrotherapy stimulation (CES) can help to relieve anxiety, agitation, insomnia, and pain (Kirsch and Nichols 2013).
    b. The first 3 months: relapse prevention and keeping the patient in treatment. Continue nutrients, herbs, and mind-body practices to reduce dysphoria and

craving. Mind-body practices also facilitate progress in individual and group psychotherapy and cognitive behavioral therapy (Brown and Gerbarg 2009, 2012; Gerbarg 2008). Augmentation with CES and neurotherapy improves emotion regulation and cognitive function and accelerates healing of brain injuries (Larsen and Sherlin 2013).

c. During the first year of abstinence, continue nutrients and herbs to support brain recovery and mind-body practices to promote emotion regulation, anxiety and anger management, and physical health. Neurotherapy and cranial electrotherapy stimulation augment neuroplasticity, cognitive function, and emotion regulation (Brown et al. 2009; Larsen and Sherlin 2013; Kirsch and Nichols 2013).

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Section IV

Behavioural Approaches

Richard A. Rawson and Marc Galanter

Behavioural Approaches: An Introduction 46

Richard A. Rawson and Marc Galanter

Abstract

Over the past 30 years, numerous empirically tested behavioral approaches to substance use disorders (SUDs) have been adopted by treatment settings. A key focus of many of these approaches is the retention of patients in treatment. This Introduction provides an overview of the chapters in this section on behavioral approaches to SUDs, including psychodynamic psychotherapy, 12-step programs, Motivational Interviewing, Cognitive Behavioral Therapy, Contingency Management, Behavioral Couples Therapy, Multidimensional Family Therapy, Network Therapy, the Community Reinforcement Approach, the Community Reinforcement Approach and Family Training, Mindfulness Meditation, and physical exercise. The final section discusses the dissemination of behavioral approaches to other parts of the world and the importance of adapting approaches in culturally sensitive ways while maintaining fidelity to the original model.

In every society where substance use disorders (SUDs) are treated in some systematic manner, behavioral approaches, including "talk therapies," are at least one element of the treatment approach. In many parts of the world where treatment for SUDs is just emerging, the behavioral treatments consist of advice-giving or commonsense generic counseling. In some areas, including the United States during the 1960s and 1970s, behavioral approaches consisting primarily of confrontational therapies designed to "break through denial" were usually delivered within the context of residential therapeutic communities. These harsh, unpleasant,

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and occasionally abusive techniques had no empirical support but were widely adopted, frequently with patient populations that had extensive involvement in the criminal justice system. During the 1980s, when these techniques were applied in outpatient settings with a noncriminal justice population, they proved to be ineffective and, frankly, counterproductive, as they resulted in poor patient compliance and low retention rates, a serious problem in outpatient treatment settings.

Over the past 30 years, a collection of behavioral interventions and approaches that were developed and evaluated in research trials have gradually been adopted into a wide variety of treatment settings. As outpatient settings have increasingly become the location for SUD services, a key guiding principle in the development of these approaches is that they should improve retention in treatment. For this reason, in many of the approaches described in this section, extensive use of positive reinforcement is emphasized to reinforce positive behavioral change, including retention in treatment.

The behavioral approaches and strategies described in the section now represent the foundational treatment paradigm for much of the SUD treatment delivered in the world. For the treatment of SUDs that have effective pharmacotherapies, including the treatment of opioid dependence with methadone and buprenorphine, these behavioral approaches are frequently employed in combination with these medications. For other SUDs, such as stimulant dependence, these approaches represent the only empirically supported techniques currently available. A limiting factor in the rapid dissemination of these approaches is that a significant training effort is needed for the successful transfer of the knowledge and skills needed to deliver these treatments. An ongoing challenge in the international dissemination of these approaches is balancing fidelity to the evidence-based principles and methods of the approach, while allowing for adaptation to the context and values of new cultures. These training and adaptation issues are covered within this section.

Section IV includes a comprehensive set of chapters on the behavioral approaches that have been developed and evaluated for the treatment of SUDs. Psychodynamic psychotherapy has long been used to understand how people use drugs and alcohol to modify hedonic states and self-regulate moods. Khantzian describes how drugs and alcohol are used to cope with suffering and emotional pain. He emphasizes the importance of the therapeutic alliance as an important element in promoting change and describes the key elements of this alliance as kindness, support, empathy, respect, patience, and instruction. Donovan and Daley describe a therapeutic approach developed for the seminal study, Project Match, which promotes the engagement and use of the 12-step program of Alcoholics Anonymous (and other related self-help programs) as a method for achieving and maintaining recovery from drugs and alcohol. The chapter reviews the empirical evidence for the benefits of participation in a 12-step program and provides guidance to physicians and other professionals regarding how they can effectively encourage patients to participate in a 12-step program.

During the past 20 years, three behavioral approaches, Motivational Interviewing, Cognitive Behavioral Therapy, and Contingency Management,

have been the most extensively researched, evaluated, and widely disseminated behavioral approaches. Motivational Interviewing (MI), conceived and presented in a 1991 text authored by Miller and Rollnick, is reviewed in the chapter by Tober (▶ Chap. 47, "Motivational Interviewing and Behaviour Change in Addiction Treatment"). Motivational Interviewing is arguably the most important behavioral strategy ever developed for the treatment of SUDs, as it has been applied in a very extensive array of settings and with a wide variety of patient populations. Tober's chapter reviews the skills that are needed by therapists to effectively employ the MI approach. Clinical examples are given to illustrate the use of key MI concepts, and training and supervision strategies are described to promote the application of MI with fidelity. Lee reviews the learning-theory underpinnings of Cognitive Behavioral Therapy (CBT) and the skills needed by therapists to effectively deliver CBT. She describes the variety of ways that CBT can be applied, with specific guidelines for how sessions can be constructed. She also provides a comprehensive array of CBT models and variations as developed by various authors/researchers, and she reviews the evidence that supports the efficacy of CBT. Roll and Fruci describe the operant-conditioning rationale for Contingency Management (CM) and methods used to apply CM principles in the treatment of addiction. They review the variety of specific modifications that can be used to practically apply CM in clinical settings. Of all the behavioral approaches, CM has the strongest empirical evidence of efficacy. Roll and Fruci organize their review of the research evidence to reflect the key factors that impact the effectiveness of CM interventions. They finish their review by addressing the implementation barriers and limitations of CM.

Three of the chapters in Section IV describe behavioral approaches involving multiple participants. In many parts of the world, group therapy plays a major role in addiction treatment. McHugh, Park, and Weiss review the variety of group therapies used in SUD treatment and the data that supports the value of group therapy. O'Farrell reviews the evidence from studies conducted in the United States and internationally on Behavioral Couples Therapy (BCT). He describes some specific techniques, including couples contracts and communication exercises, as well as some of the possible limitations of BCT resulting from the training and supervision requirements needed to ensure fidelity. Multidimensional Family Therapy (MDFT) is one of the few behavioral approaches that have been evaluated in a large multisite international trial. Rigter and colleagues describe the rationale and elements of MDFT and the methodology and results of that multisite implementation trial. The chapter describes the challenges and limitations of adapting a dissemination model for a complex therapy across different cultures and languages.

Section IV also includes three chapters that describe multielement outpatient approaches. Galanter describes the rationale and elements of Network Therapy and the importance of social support as part of successful treatment. The chapter explains how networks are created and how 12-step program involvement and medication can be valuable as elements of the network. Research evidence for support of Network Therapy is provided. The Community Reinforcement Approach

(CRA) is a multielement intervention that helps patients identify rewarding behaviors in the community that can help them initiate and sustain a nondrug-using lifestyle. Smith and colleagues explain the elements of CRA and the added component of family therapy (CRAFT) that are designed to assist in developing positive relationships with significant others. The evidence to support the efficacy of CRA and CRAFT is also presented. The Matrix Model is a multielement package of CBT, patient education, 12-step involvement, and other elements designed to be used in outpatient settings. Obert, McCann, and Rawson describe the elements of the treatment model and the extensive program of dissemination of the Matrix Model in the United States and internationally.

Two innovative behavioral techniques that are generating considerable interest are Mindfulness Meditation and physical exercise. Mindfulness is a meditation practice rooted in Buddhist tradition, combined with a collection of attentional strategies and skills designed to focus the attention of the individual in the present. Marcus' chapter describes the rationale for mindfulness, the key elements in its use, the health conditions where it has been applied, and modifications that have been added to apply mindfulness to the treatment of addiction (▶ Chap. 50, "Mindfulness as Behavioural Approach in Addiction Treatment"). Mindfulness-based relapse prevention combines mindfulness with cognitive behavioral strategies and is being evaluated in ongoing clinical trials. Mooney and colleagues review the extensive set of research that documents the robust positive health benefits of exercise. Although there is limited research literature on the value of exercise as a component of addiction treatment, the chapter discusses multiple justifications for supporting the promising potential that exercise has in assisting people with addiction.

Castro and Barrera have contributed a unique chapter of exceptional importance to Sect. IV. They discuss the importance of culturally adapting behavioral approaches in a systematic manner that considers the importance of fidelity to the original evidence-based model but allows for adaptation of the model to address specific cultural issues of importance. They describe the challenges of effective language translation as well and caution about misadaptation. They use the example of how the Matrix Model, which was developed in California, was adapted for use in Mexico. And finally, Rawson, Rieckmann, and Capoccia contribute a chapter in which they describe three successful examples of how evidence-based treatments have been implemented in the United Arab Emirates, Vietnam, and Lebanon.

Motivational Interviewing and Behaviour Change in Addiction Treatment

47

Gillian Tober

Contents

Abstract

This chapter explores social and psychological routes into addiction and the naturally occurring and assisted routes to recovery. Evidence for effective mechanisms of change points to specific components of structured treatment and its delivery, practitioner behaviors, and client attributes. The extent to which these specific components are in turn contained in usually delivered treatment methods is explored. Motivational interviewing practice as a style of consultation contains a number of effective practitioner behaviors, while other important mechanisms are found in cognitive behavioral coping skills training and in socially based network treatment approaches. Examples of dialogue and of interactions with clients are given. The specification of treatment protocols in practice manual format provides the basis for training and maintaining practice standards. Supervision and the rating of competence can be based on the use of a validated practice delivery rating method.

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47.1 Introduction

For all the evidence for the effectiveness of psychosocial interventions, it is perhaps surprising that a consensus on the optimal or standard treatment, albeit with variants to suit different addiction problems, has yet to be forged. A hundred years of behavioral research has provided both the framework for understanding addictive behavior and the evidence for treating it. There is, however, the perennial challenge of translating research findings into practice, and this is further complicated by the enduring negative attitudes to people with addiction problems, a lack of consensus about the nature of addiction problems, and about who should treat them. Different countries have different expectations of the provision of care and how to intervene, some taking the view that only professionals – medics, psychologists, social workers, and allied professions – are the right people to provide treatment, others taking the view that primarily people who have had the problem themselves are the right treatment providers or that it is the criminal justice system and possibly most commonly a combination of all of these. This makes for a situation in which a shared view of the concept of good practice, let alone the specifics, can be hard to find and effective practice quite difficult to implement.

This raises the question of what is addiction treatment for. Research reports that people seek treatment because they have lost control over an addictive behavior or have a sense that they have lost control over their life. There may be greater or lesser elements of coercion involved in help seeking whether external or somehow self-imposed, and these are combined with the ambition to achieve some sort of change. Thus, there is a need to ensure that treatment seekers have a sense of being helped to reassert control, and so it follows that treatment needs to be an active, task-oriented process. Help seekers will generally have tried to reach their own solutions: they may have appealed to family and friends for help, will intuitively have tried different coping strategies, or tried various kinds of self-help and mutual aid, and turned to other forms of social capital such as religion or spiritual inspiration. The challenge is for the helping professional to build on the individual's own resources, thus harnessing the processes of "natural recovery" into treatment-assisted recovery.

47.2 Understanding the Nature of Addiction

In order to inform effective treatment plans, practitioners need to have an understanding of the way in which the addictive behavior is reinforced; decisions about where to start are based on an accurate assessment of motivation which emanates from understanding what maintains the behavior and what scope there is for change. Addiction can most readily be understood as the manifestation of behavioral phenomena which are learned and can be reversed through the principles of behavioral extinction. Rotgers (2003) and Heather and Robertson (1997) are among numerous authors describing the way that, like all behaviors, addictive behavior is

a set of responses conditioned by internal biological and cognitive cues, external social cues, modified by *reinforcers*, both positive and negative, that are also social, psychological, and biological in nature. Miller and Carroll (2006) illustrate the complexity of addiction behavior in bringing together accounts and evidence from the biological, social, and behavioral sciences. For the practitioner, distilling out those explanations that most readily account for the observed phenomena is necessary to establish a working knowledge base that will inform practice. (Russell 1971, Russell et al. 1974) demonstrated the interaction of cues, or triggers, for a typical path into tobacco-smoking behavior and the development of dependence. This gave a useful prototype for understanding how a "social" behavior becomes an addiction: first, there are social cues and reinforcers, next learning the value of pharmacological reinforcers, and finally, in the establishment of dependence, the importance of physiological sources of reinforcement. Simply put, people usually start smoking because of peer pressure and rewards and continue once they have learned to detect the stimulant effect of the tobacco; it is the neuroadaptive state that results in the perceived inability to abstain and difficulty stopping that reinforces dependent use. Orford (2001) has illustrated the application of these behavioral principles across a range of addictive behaviors. Siegel (1999) adds to this body of knowledge with empirically based explanations of the more complex observed phenomena such as the experience of withdrawal symptoms in the absence of recent drug use, prompted by previously familiar drug using environments.

47.3 What Are the Effective Mechanisms of Change?

If the way into addiction, or dependence, is well understood in terms of social learning theory, what is known about applying this knowledge to the treatment of addictive behavior? Moos (2007) argued that the same processes that protect individuals from developing addiction problems are those that are useful in helping them to recover from these problems. He described four social learning theories that identify these processes and the way they inform psychosocial treatments that have evidence of effectiveness. He identified these as motivational interviewing and motivational enhancement therapy, cognitive behavioral treatment and behaviorally oriented family counselling, contingency management, and community reinforcement. He then presented these essentially cognitive and behaviorally based treatments in sets and identified the common theoretical principles upon which they are based. Thus he argues his case, on the strength of probability, for the theory-based active ingredients of treatments that have evidence of effectiveness. The "probable common active ingredients of effective treatments" which he extracts are (a) support, structure, and goal direction, (b) provision of rewards for abstinence and planning rewarding activities that can replace substance use, (c) abstinence-oriented norms and models, and (d) building self-efficacy and coping skills. The challenge is to ensure that psychosocial interventions contain these active ingredients as the building blocks for structured treatment and for aftercare in order to ensure the maximum benefit from treatment. Moos makes the important

point that harmful side effects of treatment are not confined to pharmaceutical or invasive treatments and he estimates that about 10 % of those receiving psychosocial treatments will be harmed as a consequence of that treatment. Among the possible explanations is a loss of optimism about the possibility of change. Help seeking is always to some extent an expression of optimism about the possibility of change and having a sense of failure following help seeking damages self-efficacy, a belief in one's ability to achieve a particular goal, on which successful change depends. It is not just doing the wrong thing that can cause harm, but doing nothing, it can be argued, is equally likely to result in harm.

Michie and colleagues (2012) have used a different starting point in the search for active ingredients or the effective mechanisms of behavior change treatments, by examining practice manuals and protocols for the treatment of alcohol problems. A list of behavior change techniques was extracted and applied to the findings of the Cochrane Review of brief alcohol interventions, and associations between the effective interventions and the identified behavior change techniques were examined using meta-regression. This method yielded the finding that brief interventions which incorporated 'prompting self monitoring' were associated with larger effect sizes. This is a small finding but one that demonstrates the further potential for identifying those behavior change techniques that are likely to make a difference and should be incorporated in routine addiction treatment.

The effective mechanisms of change reported here are supported by service user accounts of what helps recovery from addiction problems. In their analysis of 1,484 post treatment session questionnaires administered in the UK Alcohol Treatment Trial (UKATT 2005a, b), Orford and colleagues (2009a) found that, regardless of treatment received, service users found talking to the therapist, belief in their progress, and the future focus of treatment to be the most useful elements of the session. In a longer-term follow-up of UKATT service users, face-to-face interviews with 397 participants from several services in different parts of the UK asked questions about the factors to which they attributed change in their drinking. These revealed that they thought social factors, the involvement of others in their treatment, motivational factors resulting from knowing the consequences of their drinking through feedback, personal factors of determination, commitment and decision making, access to detoxification and medication and feeling comfortable talking were key (Orford et al. 2009b).

47.4 In Which Treatments Can These Effective Mechanisms of Change Be Found?

In his first paper on motivational interviewing, Miller (1983) argued that it was the understanding of client motivation, based in perceived reinforcement and shifting consequences of the behavior, which would guide the practitioner in delivering good and useful practice in treating problem drinkers. Ignoring motivation, he claimed, was counterproductive, while identifying current motivation to continue

drinking, mixed feelings about it, and allowing the service user to express their own reservations about their drinking and explore the potential advantages to the service user of change might help to shift the behavioral status quo. It was a simple argument, elegantly stated and enthusiastically received. It unlocked the therapeutic paralysis that characterized attempts to treat people who lacked motivation to change and often resulted in negative attitudes to the treatment of addiction that endure in many settings to this day. Miller went on to describe how this facilitation might be done, with a set of Rogerian (Rogers 1959) principles including listening to the client, not telling the client what to do, asking for the client's perspective, and reflecting their thoughts. Miller however developed the Rogerian principles with a critical new element: he introduced the idea of direction that is of the practitioner having an agenda that focused on change and improvement in the client's health and social well-being through the medium of stopping or changing drinking. In order to pursue this agenda, Miller suggested that reflections should be selective, highlighting negative thoughts about drinking, positive thoughts about the outcomes of change, and about ability to change.

Miller's proposed style of consultation owes its popularity to the context in which it was presented: the equally popular and contemporaneous development by Prochaska and Diclemente (1984) of a model of change that described the fluctuating nature of motivation which determines continuation or modification of addictive disorders (and not just these behaviors) and drew attention to the imperative to address this motivation if change was to be facilitated. Miller operationalized a method of helping people move forward toward making a decision to change, instead of becoming entrenched in arguments for continuing the behavior (manifest as denial, rationalization, or justification).

Thus, motivational interviewing with its support for the client, its structure, and goal directness embodies effective mechanisms of change outlined by Moos. Furthermore, it is designed to increase self-efficacy by exploring the client's beliefs in their ability to change and the resources they need to enhance these beliefs. More recent research on what happens in motivational interviewing by Amrhein and colleagues (2003) deepens our knowledge of how to harness the method to optimize change by ensuring that an expression of commitment to change is the goal of the motivational dialogue. In their analysis of the discourse between practitioners working in a motivational interviewing style and their clients' responses, Amrhein et al. (2003) found that the statement of a commitment to change made by the client predicted that change was more likely to occur than when no such statement of commitment was made. The contribution of this work was to distinguish different kinds of "change talk," where the client expresses the desire to change, the ability to change, the need to change, and reasons for change, and identify "commitment talk," defined as the statement of an intention to change. They found that it was the presence and the strength of this commitment talk or expressed concrete intention to change which predicted that change was more likely to occur. Apodaca and Longabough (2009) reviewed the mechanisms of change in motivational interviewing and their findings support the importance of client change talk that

expresses intention to change. How the practitioner achieves this is less specifically defined; but one thing seems clear. Hours are spent in the average clinic or counselling room talking about the importance of change, that it needs to happen, that it ought to happen, and that life would be so much better if it did happen. Talking about change and its benefits is not enough. Making a commitment to change is the point that needs to be reached in order for change to have a chance of happening, at least in the consultation or counselling setting.

In general terms, the weight of the evidence points to the likelihood that motivational interviewing as a style of consultation enhances treatment engagement and *treatment adherence* (Hettema et al. 2005). People are more likely to come into addiction treatment where they experience being listened to and more likely to stay where they feel that their own thoughts and feelings are being addressed. What the practitioner should be trying to achieve is clear, but how exactly they might achieve this is less clear and the evidence on the specific components of motivational interviewing that make a difference is equivocal. Apodaca and Longabough (2009) claim that practitioner behaviors thought to be inconsistent with motivational interviewing, described as confronting, directing, and warning, were found to be associated with worse outcomes across treatment for problem drinking and illicit substance use, while Miller and colleagues (1993) in comparing motivational interviewing with a confrontational style of treatment as usual found that the latter tended to result in in-session conflict, which in turn predicted worse drinking outcomes up to 2 years after treatment.

Based on these findings, the core skills of motivational interviewing which facilitate the accurate assessment of motivation, enhance motivation to decide upon and pursue a change goal, are thought to be characterized by open questions and selective reinforcement:

If you want to assess the individual's motivation regarding their drinking, ask them, and do it in such a way as to communicate interest in what they have to say; avoid telling them what you think, either verbally, in the tone of your voice, or in your body language. This is open questioning. It makes intuitive sense and it is a learned behavior in itself, one that is difficult for clinicians who are trained to make differential diagnoses by questioning whether a list of things is present or not:

Tell me about your recent drinking
What has recently happened when you have been drinking this amount?
What are your thoughts about this?
What would you like to be different?

This second skill is more difficult for the nondirective counsellor, or the "person-centered" counselling practitioner where the counsellor is required to follow any agenda set by the client; rather it is the skill of contingent or selective reflection. The task is to reflect the things that are relevant to the question of drinking, or drug use, or the health behavior that justifies the conversation. The difference between reflection in this style of motivational dialogue and nondirective reflective listening is that selective reflection facilitates the forward movement of the dialogue in a combination of the directiveness and support to which Moos referred as active mechanisms for change:

You feel ill after drinking that much
You dislike the looks that people give you in the street
You are fed up with being treated as being unreliable
You want to be able to look after the children
You think that your drinking is getting in the way of that

The combination of open questions and selective reflections enables the practitioner to move the dialogue forward through change talk about their desire to change, to reach the point of an expression of optimism about the possibility and outcomes of change, and then a commitment to change. But how does this work? Why do people change their view of their drinking? Some studies have shown that the provision of feedback that is objective and personalized, such as described in the Drinker's Check-up (Miller et al. 1988) which formalized the process of heightening concerns about use, a key component of change talk, is what makes motivational interviewing effective. Thus, neuropsychological tests can be useful, as demonstrated in Miller et al.'s study and liver function tests as demonstrated in the UK Alcohol Treatment Trial (2005a). The distinguishing features of using feedback from test results in a way that is more likely to enhance motivation for change are that the tests themselves are objective and valid, produce results that are measurable against population norms or well-functioning people, are personalized, and are presented in a manner that enables the recipient to understand both their meaning and their potential for change. Importantly, they need to be perceived to be a result of drinking, drug use, or whatever the target behavior is and to be improvable as a result of a change in the target behavior.

Avoiding confrontation and conflict in the consulting room and establishing collaborative working with the client toward a common goal are supported by research on the therapeutic alliance, where collaboration between therapist and client encourages a feeling of mutual respect enabling the therapist to be a helping agent and creating conditions for the client to explore opportunities and enhance self-efficacy for change. Those elements of communicating respect and positive regard, listening to the client, and agreeing the goal of treatment, which are shown to make a difference, highlight the contribution of the motivational interviewing method in the operationalization of this professional conduct or the way to achieve this therapeutic alliance.

The same skills are used throughout the next steps of the process: when motivation to change has been heightened, the decision to make a commitment to change is prompted; thus, if there are, for example, negative thoughts about drinking or drug use and positive thoughts about stopping, a goal can be formulated in a dialogue that follows the open question: *How would you like or prefer things to be*? and then using selective reflections to narrow down the response to a clearly articulated goal. This articulation of the goal may be the result of statements like *I want to stop arguing with my partner*; *I want to stop taking time off work*; *and I want to be someone my children can look up to*, when the practitioner asks the further question about how this can be achieved, eliciting the response *I want to stop drinking*. The requirements of the goal are that it is specific and well defined, measurable, realistic, and achievable and has a time frame attached to it.

This is well-trodden territory, and yet many of these key elements are often missing in addiction treatment. It helps the practitioner as well as the service user to stay focused if the goal is regularly reviewed and restated, enabling repeated assessments of motivation to change: change "but not just yet" is weak commitment, and so are loosely defined goals, unrealistic goals, and goals that cannot be measured. It is not difficult to check that the key criteria are met.

How to implement the behavior change required to achieve the goal takes us into the territory of applying effective behavior change techniques, as the next step involves making short-term behavior change plans. Thinking about the rest of life is too difficult. Listen to the mantras of followers of the 12-step approach. *One day at a time* is popular because it is manageable. In describing the implementation of the active mechanisms of change in behavioral treatments of addiction, Carroll and Rounsaville (2006) point to increasingly robust evidence for key components. Skill rehearsal involves the client trying out the new behavior and rehearsing the thoughts that precede and accompany the behavior. In reviewing these rehearsals, one can decide whether they are realistic approximations of what can happen. Next comes the setting of homework, or skills practice in vivo; the definition of tasks needs to be concrete and specific for time and place; and then monitoring the method. The effectiveness of giving homework is in the monitoring and reporting back of it, without which, the research tells us the setting of homework makes no difference to the learning of new skills.

47.5 The Social Focus of Treatment

People with social networks of family and friends who are supportive of change have a greater chance of changing than those whose social networks support heavy drinking or drug use. Some of the behavioral interventions based on recruiting and mobilizing such a support network are the community reinforcement approach (Meyers and Smith 1995), network therapy (Galanter 1993), and social behavior and network therapy (Copello et al. 2009). While all of these have an evidence base, they are not universally practiced; they do, though, provide a strong argument for moving away from individualized treatment and ensuring that every intervention is delivered to an individual in a social network.

The process of getting other people involved, people who are available, willing, and able to help put the plan into practice, involves a set of skills not always familiar to the addiction practitioner trained in delivering individually based treatments. This approach has been identified repeatedly by clinical researchers: McCrady (2006) emphasizes the importance of the family in each step of the helping-seeking journey. Like Moos, she describes the central role of the family in protecting against or increasing the risk of substance misuse problems, thus highlighting the opportunity for harnessing their support in recovery. The wider search for sources of support beyond the family was at the heart of the development of social behavior and network therapy (Copello 2007) in which "think network" is a key practitioner skill. Good network plans are made by people who want to work together, who want

to give and get support from each other, and who want the same outcome. The pharmacological components of treatment and compliance with them can be incorporated into the network plan, and the behavioral principles of rehearsal and reporting back and modifying behaviors in the light of feedback can be pursued.

The importance of positive role models is addressed in the network approach. A well-functioning network will include modelling of behaviors and positive experiences of rewarding activities not associated with drinking or drug use. If such role models are to be found outside the network, for example, in a local Alcoholics Anonymous meeting, or other mutual help fellowship, the network can provide the support to make the initial contact which people can find so difficult. Treatment staff have variable attitudes to encouraging attendance at and affiliation with mutual aid when the evidence for their effectiveness is gathering momentum.

In each of the sets of skills described, the active mechanisms identified by Moos and others are included. Thus, the network-based support, change plan, and relapse prevention plan enhance self-efficacy (there are always people there to help) and coping (everyone learns new coping skills in the network); it is focused on the goal and support is explicit; its direction is enshrined in its future focus (how are things going to be different from now on?). This set of skills, a combination of motivational enhancement for change and behavior change skills delivered in a network supportive of change, can be adopted in a variety of addictive behavior change settings, whether there is an addiction problem in isolation or in combination with other disorders, at each stage of behavior change, decision making, planning, and maintenance of change, in the context of pharmacological, psychological, and social interventions, and whether the treatment goal is abstinence, control, or harm reduction.

47.6 Treatment Protocols and Their Inclusion in Manuals to Guide Practice

Effective methods for helping the client to change their addictive behavior have been incorporated into treatment manuals, self-help materials, training guides, and numerous forms of brief interventions. Let us get the problems with treatment manuals out of the way. The first is that they are not often published and so are difficult to find. Where they have been developed as part of clinical trials, they are likely to be placed in the public domain. The three treatment manuals which were used in Project MATCH: Motivational Enhancement Therapy (Miller et al. 1992) which gives useful examples of worksheets for delivering feedback from tests and monitoring behavior; Cognitive Behavioral Coping Skills Training (Kadden et al. 1992) combines the core and elective sessions of behavior change treatments with adaptable worksheets; and Twelve Step Facilitation (Nowinski et al. 1995) focuses on an introduction to the 12-step philosophy and practice and encouragement to embark on that recovery journey, all available from NIAAA. Treatment manuals used in subsequent US trials for different substance dependencies such as cocaine, heroin, and cannabis are published by the US Clinical Trials Network via Internet media.

Monti et al. (2002) have developed their manual for the treatment of alcohol dependence and incorporated developments in clinical research. Manuals may also be published as books giving extensive examples of practice (e.g., Copello et al. 2009; Tober and Raistrick 2007).

Rigid adherence to manual-based protocols is counterproductive. Indeed in their meta-analysis, Hettema et al. (2005) found that motivational interviewing was more effective when practiced without a manual. The strongest message to come from the use of manuals in guiding treatment is that they are useful for ensuring practitioners adhere to a structure, the prescribed content and style of treatment delivery, but they are not useful when practitioners follow them "blindly." Manuals do not compensate for lack of knowledge and experience, and the best use of them is by more experienced practitioners. Every treatment session needs to be adapted to the individual client, their motivation, social circumstances, and the severity of their condition, and a good manual will be designed to be used in this way.

Manuals can provide the basis for detailed scrutiny of practice where video or audio recordings of practice form the basis for detection and analysis of the components of treatment and the quality of their delivery. There are validated methods to rate competence and practitioner adherence to practice protocols. These can be used for the dual purpose of independent rating of treatment delivery and for supervision to improve and maintain good practice. Such ratings ensure that the active mechanisms of change are present and make it possible to identify differences in practice and explore whether and perhaps why practitioners successfully engage service users in treatment and change (see, e.g., Tober et al. 2008). Practitioner competence is the key to effective treatment; time and money can be saved by focusing on just doing those things that make a difference.

47.7 Who Treats Addiction Problems?

Everybody who works in health and social care can contribute to addictive behavior change. Successful outcomes are not just the result of formal treatment but also the accumulated effect of small but positive "nudges" toward motivation to change. There is no sense in thinking that busy staff with other responsibilities on their minds can screen or deliver brief treatments to people with drinking or drug problems: the liver transplant surgeon, the nurse looking after the patient with pancreatitis, the emergency room doctor dealing with trauma, and the social worker handling a child protection case can all see where drinking or drugs are causal agents. What these staff need to be able to do is help to build motivation; in part, this is by working in a motivational style, that is, being empathic, using open-ended questions where possible, and reinforcing change talk, and it is also by simple motivational enhancement techniques like asking a question such as "what difference do you think your drinking is making?". Making the specialist addiction services as available as is possible is going to be more fruitful than trying to get staff with other jobs to do to screen and treat people with addiction problems. Promoting optimism for and confidence in the outcomes of specialist treatment may

be the one ingredient necessary to encourage generalists to refer to specialists in addiction. It is up to the specialists to help others to have a positive experience of helping people with addiction problems and also to understand that these individuals can be very challenging when they present in health and social care settings that are not geared up to deal with them.

47.8 Implementing Effective Treatment: Getting Competent Practitioners

What are the necessary conditions for being a competent specialist addiction practitioner? Knowledge of the nature of addictive disorders, as well as understanding of the experience of having an addiction disorder, gained from listening to people who have them, and of the illnesses and other consequences that result from them are the foundations for accurately assessing the problem and its various consequences and making the right treatment decisions. Understanding the behavioral principles that drive the addiction itself and the evidence-based effective mechanisms of change provides the building blocks for the specific intervention. Utilizing a manual that incorporates these and gives guidance for practice that is context specific and culturally relevant gives the prototype against which to measure competence and will enable practitioners to maintain treatment protocol adherence, once this has been established through training followed by supervised practice and the rating of competence (Tober et al. 2005).

Those practitioners who are perceived to be authoritative in their knowledge of the problem and their knowledge of effective treatment and who are perceived by the client to be competent in effective treatments will be likely to deliver better outcomes, so the research has shown. Knowledge and then practice of behavior change techniques, moving from the key components to the complex business of practicing in addiction treatment settings, are not as simple as the description of skills suggests. Addiction problems are by definition complex, and people present with multiple complexities such as dual diagnosis with mental illness, physical illness, pregnancy and child care concerns, and criminal and other antisocial behavior. Competence will be achieved through continually supervised practice in a supportive environment where there is an ambition to implement the evolving science as a matter of routine.

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Cognitive Behavioural Therapies for Substance Use Problems

48

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Contents

Abstract

Cognitive behavior therapy (CBT) is an umbrella term that describes a group of therapies, that although many in number and broad in their approach, have in common a focus on thoughts and beliefs (cognitions) as the central driver of, and the solution to, effective emotion regulation. The early CBT models (sometimes referred to as the "first wave") focused primarily on response to stimuli and included the theories of B.F. Skinner and Joseph Wolpe. The "second wave" introduced the concept of cognition into the behavioral models; the most well known of these models were developed by Aaron Beck (Cognitive Therapy) and Albert Ellis (Rational Emotive Behavior Therapy). The "third wave" models are primarily the mindfulness-based cognitive therapies, although a range of other integrative therapies, such as Schema Focused Therapy and Emotion Focused Therapy, are sometimes included in the group of newer CBT models.

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This chapter describes how these models work and how they have been adapted to substance use treatment, ranging from intensive to brief and low-intensity interventions. The evidence shows that CBT is one of the most effective interventions for substance use issues, as well as for co-occurring substance use and mental health problems. Traditional (second wave) CBT has the most evidence for its effectiveness, and the mindfulness therapies have a growing body of evidence that shows that they potentially have similar outcomes for substance use disorders. CBT has been adapted and applied across a range of cultures and countries.

"We are what we think. All that we are arises with our thoughts. With our thoughts we make the world."
Shakyamuni Buddha

48.1 Introduction

Cognitive behavioral therapy (CBT) is an umbrella term that encompasses a large number of therapies. Although many in number and broad in their approach, they have in common a focus on thoughts and beliefs (i.e., cognitions) at their theoretical center.

These therapies are not just a collection of random strategies but are based on a coherent theory that drives the techniques that now form the collection of CBT approaches. Due to its important role in treatment, CBT has become a core competency for alcohol and other drug workers.

This chapter introduces the range of therapies that come under the CBT banner, briefly describes their underlying theoretical structures, and summarizes the evidence for their effectiveness.

48.1.1 A Brief History of CBT

The history of CBT is important to an understanding of its current form and application, since it encompasses a very broad range of therapies that have in common a focus on cognitions and their influence on behavior.

From the late 1800s to the 1940s, psychotherapy was dominated by the theories and therapy of Sigmund Freud – referred to as psychoanalytic psychotherapy or psychoanalysis – and a number of other therapies that grew out of, and diverged from, psychoanalytic psychotherapy, such as dynamic psychotherapy and Gestalt therapy. These therapies have a focus on unconscious conflicts and processes and on the dynamics between the therapist and client. Therapy by these methods is usually offered several times a week or even daily and is expected to take several years to be effective. Over time, other briefer versions of these therapies have developed, based on similar theoretical hypotheses.

In the 1950s, something of a revolution took place in psychotherapy. Psychology more broadly had begun to develop itself into a scientific discipline with a focus on the scientific method, and psychoanalytic therapy came under public criticism from people like Noam Chomsky for its lack of scientific rigor. Psychoanalytic therapy adapted and changed in response, but at the same time another branch of psychology began to form, driven by scientific enquiry: the behavioral therapies.

Although the term "behavior modification" was used much earlier by Thorndike and "behaviorism" was described by John B Watson in the early stages of the twentieth century, the real development of behavioral theories as applied to modern practice began in the 1950s, drawing on earlier theories of classical conditioning (Pavlov 1927).

By the 1950s, B.F. Skinner in the USA and Jack Rachman and Hans Eysenck in the UK began looking at environmental factors that could shape behavior and developed treatments based on operant conditioning, such as contingency management (a structured system of rewards for achieving treatment goals). Around the same time, Joseph Wolpe began experiments looking at changing behavior through reinforcement using rewards and punishments, the results of which led to the development of Behavior Therapy (Wolpe 1973).

These therapies were all based on the theory that a response (behavior) was triggered by stimuli (learned external triggers). This group of early behavioral therapies is often referred to as "first wave" behavioral therapies.

The "second wave" came in the 1960s via two psychoanalytically trained therapists. Aaron Beck ("Cognitive Therapy"), a psychiatrist, and Albert Ellis ("Rational Emotive Behavior Therapy"), a psychologist, both came to believe that something other than psychoanalytic ideas of unconscious conflict was the cause of their patients' problems and theorized that there was also something deeper than just the "stimulus" and "response" of the behaviorists.

Second wave models described a process, often not in complete awareness, by which an individual interprets a stimulus and then uses that interpretation to mediate a response – that is, thoughts and beliefs. The intervention, therefore, is focused on assisting a person to become more aware of, understand, and analyze his or her thoughts and beliefs that drive a response in a given situation and then to consider whether the thoughts are (a) true or irrational and (b) helpful or unhelpful.

As the second wave theories developed, they drew ideas from cognitive psychology (Neisser 1967), which described how sensory input is received, transformed, and interpreted by an individual, and from social learning theory (Bandura 1977), the latter of which puts additional importance on the context of learning, particularly through concepts like modeling and observational learning.

The "third wave" of CBT has most recently developed with the mindfulness-based therapies such as Dialectical Behavior Therapy (DBT) (Linehan 1993), Mindfulness-Based Relapse Prevention (MBRP) (Bowen et al. 2010), Mindfulness-Based Cognitive Therapy (MBCT) (Segal et al. 2002), and Acceptance and Commitment Therapy (ACT) (Hayes and Strosahl 2011). These therapies are based on a similar theoretical understanding of the function of thoughts and beliefs, and while they focus on increasing awareness of thoughts, they differ from

traditional CBT approaches in that, rather than analyzing or controlling them, the aim of therapy is accepting the thoughts and letting them pass.

This chapter focuses on the second and third waves of cognitive behavioral therapies.

48.2 The Cognitive Behavioral Approach

48.2.1 Description of the General CBT Approach

Like any other therapy, CBT is not merely a manualized set of techniques but is based on well-researched theoretical models that share the underlying assumption that our thoughts, behaviors, and emotional reactions are learned and that the path to well-being is through managing thoughts and beliefs in some way. The fact that CBT is often manualized is an artifact of its structured and scientific approach rather than a fundamental part of the approach. There is some evidence that a single-focused approach is more effective than an eclectic one (e.g., Moos et al. 1999), suggesting that a sound basis in a single therapy is most effective. Therefore, it is important to understand the underlying theoretical structure of CBT, not merely the strategies or techniques, to apply the interventions effectively.

Strategies to manage thoughts and beliefs may differ between different styles of CBT. For example, in Cognitive Therapy, change is facilitated through strategies to analyze and change thoughts, while in mindfulness approaches the focus is on becoming aware of, and accepting, thoughts.

In general, cognitive and behavioral therapies are relatively brief (usually 10–20 sessions), and even briefer therapy versions have been developed that are designed for delivery in between 1 and 6 sessions.

48.2.1.1 General Assumptions of CBT Approaches

A number of assumptions are specific to CBT (Mitcheson et al. 2010), including:

- Substance use and dependence is a learned behavior, emerging over time, and can therefore be "unlearned."
- Substance use and dependence is seen within a context of environmental influences, including the influence of family and friends, availability of substances, and sociodemographic circumstances.
- Substance use and dependence is developed and maintained by particular thought patterns and processes.

Although CBT models understand that substance use and dependence is complicated by genetic, biological, and temperamental factors, these are considered risk factors rather than determinants. Much in the same way, certain people may have a biological or genetic history of heart disease that puts them at higher risk of heart problems, but environmental and learned factors such as eating habits, ability to control stressors, and exercise can prevent or lead to the development of a heart condition.

Beck (2011) outlined ten principles that underlie CBT:

1. CBT requires a sound therapeutic alliance.
2. Collaboration and active participation by clients in their own treatment is essential and is an important vehicle to developing a positive therapeutic alliance.
3. CBT is goal oriented and problem focused. While building the whole person is important, addressing the client's immediate goals through developing problem-solving skills is the initial focus of treatment.
4. CBT emphasizes the present, at least initially. This is especially important because, for many substance using clients, focusing on resolving past difficulties, especially those associated with the development of substance use, may be of little benefit unless the day-to-day issues of drug use are addressed (Mitcheson et al. 2010). For example, it is difficult to address childhood trauma, which may have contributed to the development of a drug problem, if the client is attending sessions intoxicated.
5. CBT teaches the client to be their own therapist and emphasizes relapse prevention. CBT helps clients to develop skills in self reflection and self-management during sessions, but the emphasis of therapy is what happens outside therapy; hence, "homework" is important.
6. CBT is relatively brief and time limited.
7. CBT sessions are structured but not inflexible. Structure helps the process of therapy and also models a structured way of thinking and being for the client. Clients with substance use issues sometimes have chaotic and disorganized lifestyles that enable and maintain further substance use.
8. The focus is on thoughts and beliefs, linked to the idea of developing the client as their own therapist through learning to manage their thoughts.
9. A variety of strategies are employed to address thinking, mood, and behavior management skills. All these strategies are drawn from a clear theoretical base.
10. CBT is based on a constantly evolving formulation, based on the scientist-practitioner approach.

48.2.1.2 The Scientist-Practitioner Approach

CBT is driven by the scientist-practitioner approach. That is, the practitioner applies the scientific method to understanding and addressing client issues. Therefore, in-session CBT is based on a constantly evolving cognitive behavioral case formulation that develops hypotheses that are collaboratively tested. This is referred to as "collaborative empiricism."

The case formulation is a way to put relevant information from an assessment into a guide for treatment. It looks at all factors that contribute to the client's presentation and how these might be addressed to meet the client's goals.

The "7Ps" is one method to understand the client's issues and develop a case formulation:

1. Presenting problem(s): What is the problem the client presents with? Are there issues that have been identified through the assessment? Is the client prepared to work on their presenting problem, or is it better to focus on a less salient problem initially?

2. Pattern and onset: What is the current pattern of substance use, how did it start, and how do the pattern and history of use impact on current strengths and vulnerabilities?
3. Predisposing factors: What are the client's vulnerability and risk factors (e.g., family history of drinking or drug use; trauma; or neglect in childhood)? Understanding these risk factors can help tailor treatment and indicate the need for referral. For example, if a client has a history of trauma, ensuring that treatment is "trauma informed" and does not inadvertently re-traumatize the client is not only client sensitive but can also assist in reducing the client's risk of relapse.
4. Precipitating factors: What are the client's immediate triggers to substance use (e.g., anxiety or stress, external cues)? Identifying immediate- and longer-term triggers for use can focus treatment substantially.
5. Perpetuating factors: What variables maintain substance use (e.g., homelessness, friendship circles, dependence)?
6. Protective factors: What protective factors does the client currently have at their disposal (e.g., friendship circle, attendance at meetings, clear insight)? These protective factors can be used to support treatment and can also be further developed in treatment.
7. Prognosis: What is the likely outcome of treatment for this client? Prognosis helps practitioners understand how to modify treatment options to realistically address client's needs. For example, if the client is highly likely to relapse given the current circumstances, harm reduction strategies may be most helpful at this stage, while trying to engage the client in 12-step groups may be setting them up for failure.

48.2.1.3 A Typical Session

Typically, CBT uses a structured session plan, and the session can be considered in three or four sections. Within those sections, the work is tailored to the client's needs, so the session format is both structured and flexible.

Carroll (1998) recommends the 20-20-20 rule: 20 min on review of the week, homework tasks, and issues arising during the week; 20 min on discussion and practice of a particular skill or topic linked to an issue from initial assessment or something that has arisen during the week (e.g., "since you've had a couple of close shaves this week, I thought we'd talk about high-risk situations today"); and then 20 min on recapping the session, agreeing on homework tasks, and planning for the next week. In reality, sometimes the middle 20 min takes up slightly more time than the first and third 20 min, and it may become a 15-30-15 rule.

Mitcheson et al. (2010) use a 4-part structure: (1) setting the agenda and recap of previous session, (2) dealing with the specific agenda items (i.e., the focus of the session), (3) planning for the next session, and (4) session review.

Structure is necessary because often clients do not have well-developed skills in structuring their own lives and this serves as a model to assist them to learn these skills. Therefore, generally in CBT, the structure is outlined to, and agreed with, the client at the beginning of each session. This practice is referred to as "setting an agenda".

It is important to note that "structured" does not necessarily mean "inflexible," and if issues arise, they should be incorporated into the agenda as appropriate. The purpose of the structure is to help the client learn how to structure activities themselves and so that it is clear to both the client and the practitioner what the focus is for the session. The structure is not rigid, and practitioners still need to use their clinical judgment and skills to determine what happens within the structure and when it may need to adapt to the immediate circumstances.

48.2.2 Application of CBT to Alcohol and Other Drug Treatment

48.2.2.1 Relapse Prevention

The original focus of Relapse Prevention (RP) (Marlatt and Gordon 1985) was to address the important issue of relapse after cessation of substance use (Marlatt and Donovan 2005), although it is now used in cases of controlled use and among alcohol and other drug users who are not yet abstinent.

The primary focus of RP is to identify and understand "high-risk situations" (which may be locations, people, or emotions) and for the client to develop behavioral coping strategies for those situations. RP distinguishes between a "lapse" (initial use after abstinence) and a "relapse" (continued use after abstinence). The main goals of RP are to (a) prevent relapse from occurring and (b) if a "slip up" does occur, to prevent the lapse from becoming a long-term relapse. Salient beliefs about the effects of using alcohol and other drugs, such as "I can only relax if I have a drink," can increase the risk of lapse and relapse in specific situations, for example, during periods of high stress (Mitcheson et al. 2010).

The cognitions and emotions underlying a lapse, such as perceived loss of control, guilt, and self-blame, may lead to an "abstinence violation effect" (AVE) (i.e., yielding fully to using substances – "I've blown it so I might as well use whatever I want. . ."). Several early studies have shown a link between the AVE and relapse. If the person attributes the lapse to a moral or personal failure, AVE may be activated and relapse is more likely, but if the person sees the lapse as external and controllable, relapse is less likely. Therefore, self-efficacy (one's belief in one's ability to achieve a goal – in this case abstinence or controlled use) and expectancies (beliefs about the effects of alcohol and other drug use) become very important and are one of the main targets of treatment.

In the RP model, negative emotional states are considered to be one of the main predictors of relapse. Therefore, developing emotional regulation skills is an important component of preventing relapse (Witkiewitz and Marlatt 2004).

48.2.2.2 Cognitive Therapy

Cognitive therapy of substance abuse was first developed by Aaron Beck et al. (1993); based on his general Cognitive Therapy (CT) model, CT is now the psychological treatment of choice for a wide range of psychological and psychiatric problems. Cognitive Therapy is often used interchangeably with the term cognitive behavior therapy, but the latter refers to the collection of CBT interventions,

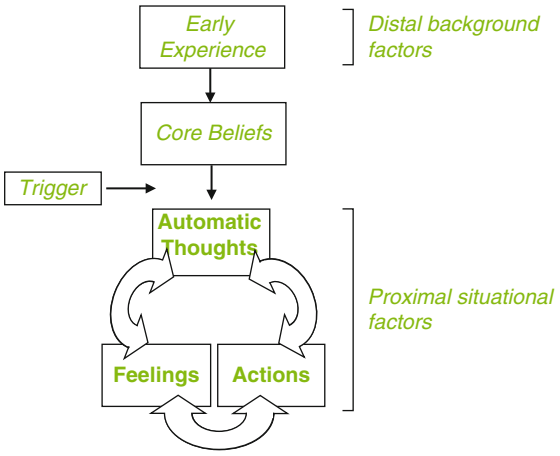

Fig. 48.1 General Cognitive model

including CT; Cognitive Therapy is a type of CBT. Typically, in the literature an intervention described as "cognitive behavior therapy" is a pure or modified form of CT or sometimes a pure or modified form of RP.

Not dissimilar to RP, the theory of CT focuses on "proximal situational factors," such as cognitive, behavioral, emotional, and physiological variables that are immediate triggers for substance use, and "distal background factors," such as personal history, long-standing cognitive and behavioral variables, and personality traits that provide a context or set of vulnerabilities for substance use and may act as maintaining factors (Wenzel et al. 2012).

A general Cognitive model is outlined in Fig. 48.1. In this model, early experience develops our fundamental beliefs about ourselves and the world (distal background factors). These beliefs are referred to as "core beliefs" or "schemas" and can be positive or negative. At various times, our core beliefs may be triggered by people, places, or events (proximal situational factors) that lead to "automatic thoughts" or the day-to-day thoughts that drive our feelings and behaviors. Everybody's early experiences are different, even those from the same family, and their core beliefs will therefore be highly individualized.

48.2.2.3 Coping Skills Therapy

Coping skills therapy (CST) was developed by Monti and Rohsenow (1999), initially in conjunction with cue exposure therapy, and has many similarities to relapse prevention. Like RP, CST is based on social learning theory but focuses more heavily on learning behavioral coping skills and less on cognitive skills, in high-risk situations. It also teaches specific social skills both to improve relationships that have been damaged through alcohol or other drug use and to help develop healthy, nonusing social networks.

Monti also used cue exposure therapy to extinguish alcohol-related cues and to enable an environment to test out coping skills (Monti and Rohsenow 1999). Although there are several positive studies linking cues to relapse, cue exposure

has not shown the same effectiveness in substance use treatment as it has in other mental health areas, such as post-traumatic stress and obsessive-compulsive and panic disorders (e.g., Kavanagh et al. 2006), and CST is more commonly practiced as a stand-alone treatment.

The four main components of stand-alone CST are relapse prevention training, social and communication skills training, training in coping with urges and cravings, and mood management. Project MATCH, the largest alcohol treatment outcome study, used a modified CST as the cognitive behavioral arm of the study (Kadden et al. 2003) and found modified CST equally as effective as motivational enhancement and 12-step facilitation.

48.2.2.4 Brief CBT

A number of brief CBT interventions have been developed, primarily based on relapse prevention or coping skills therapy. In general, brief CBT interventions are best utilized for moderate- to high-risk use and with people who are dependent but are not ready to engage in intensive treatment. They have been found to be effective for a range of substance users, including those who are dependent.

In Australia, Baker et al. (2003) developed a two or four session intervention for amphetamine users that combined Motivational Interviewing with brief RP, including coping with cravings and lapses, controlling thoughts about using (triggers, seemingly irrelevant decisions, and pleasant activity scheduling), and preventing relapse (refusal skills and relapse planning). Methamphetamine users can be difficult to engage and retain in treatment, and a briefer intervention may be more desirable for this group.

A six-session intervention for cannabis dependence (Copeland et al. 2001; Rees et al. 1998) has also been developed in Australia, using a combination of Motivational Interviewing and CBT. Sessions include goal setting, planning to quit, dealing with lapses and relapses, refusal skills, managing withdrawal, and cognitive and coping skills.

In addition, a range of brief therapies (one to two sessions) and brief interventions (5–20 min) for moderate- to high-risk drinking have been developed, based on social learning and CBT principles, including coping skills training and relapse prevention (see Substance Abuse and Mental Health Services Administration 2012).

48.2.2.5 Low-Intensity CBT

"Low-intensity" mental health interventions are those that are less intensive for the practitioner or service and sometimes, but not necessarily, less intensive for the client. They can be delivered face-to-face, usually by nonspecialists in drug treatment, for example, by medical practitioners delivering screening, brief intervention, and referral into treatment (SBIRT), and through psychoeducational groups and "advice clinics." They may also be delivered using a range of remote and self-directed technologies, such as books and paper-based materials, CD-ROMS and computers, and online media such as the Internet (NICE 2011).

Low-intensity interventions have the advantage of increasing reach, access, flexibility and responsiveness, patient choice, and cost-effectiveness

(Bennett-Levy et al. 2010) and can be used to address a range of substance use problems from prevention to tertiary treatment. Cognitive behavioral therapies are ideally suited to the low-intensity environment because they are typically brief, structured, and easily manualized.

There have been a number of different types of low-intensity interventions developed in recent years. Advice clinics, for example, operate in mental health services in the UK (White 2010) as a one-off 30-min appointment with a clinician.

Guided self-help CBT (Kenwright 2010) involves either paper-based or Internet-based self-directed learning materials that are supplemented by lower-intensity guidance from a practitioner as required. The practitioner is available to answer questions about the material, but otherwise the client works through a brief program essentially on their own.

While brief telephone counseling has been accessible for decades in some countries, more recently there has been development of a number of similar services using email and online media. An online service in Australia (counsellingonline.com.au), for example, uses live online chat-style environment to provide brief interventions for people with substance use problems. An early review of the service showed that the types of clients and the types of presenting issues are markedly different from telephone counseling, with younger people and methamphetamine users making up a greater proportion of online clients (Swan and Tyssen 2009), suggesting that these types of interventions do indeed increase reach and access to hard-to-reach populations.

In addition, interventions have been developed for SMS (mobile phone text messaging) (Shapiro and Bauer 2010), mail (Kavanagh et al. 2010), and online-facilitated peer support (Griffiths and Reynolds 2010) (see www.theshedonline.org.au for an example).

48.2.2.6 "Third Wave" Therapies

Broadly, third wave therapies integrate mindfulness theory and practice with CBT, although Schema-Focused Therapy (SFT) (Young et al. 2003), originally developed for personality disorders, is also sometimes considered in the third wave. SFT is an integration of CBT, gestalt, psychoanalysis, and psychodrama theories and strategies. There has been some attempt to use SFT for co-occurring personality and substance use disorders (Ball and Young 2000), but it is not widely used in substance use treatment.

Mindfulness approaches focus on the cultivation of acceptance of negative thoughts and feelings and strategies to regulate affect. Some have suggested that there is a substantial difference between mindfulness-based and traditional CBT, enough to consider them as a new therapy, but Hoffman et al. (2010) have noted that the (limited) evidence available suggests that the mechanisms of action between new and traditional CBT approaches are more similar than different.

Among the range of mindfulness-based cognitive therapies, only one has been developed specifically for substance use disorders. Mindfulness-based relapse prevention (MBRP) is an 8-week outpatient program that incorporates traditional relapse prevention strategies with mindfulness practice such as acceptance and meditation (Bowen et al. 2009).

Other mindfulness-based interventions that have been trialed with substance users include dialectical behavior therapy (DBT), acceptance and commitment therapy (ACT), and mindfulness-based cognitive therapy (MBCT).

DBT was originally developed for borderline personality disorder (BPD) and is a combination of standard CBT strategies for emotion regulation and four mindfulness-oriented modules of mindfulness, distress tolerance, emotion regulation, and interpersonal effectiveness (Linehan 1993). It has been recommended by its developers as most suitable for very complex substance use disorder presentations, including people with co-occurring substance use and BPD, substance use disorder and chronic suicidality, and substance use disorder that has not responded to traditional CBT over time, especially if emotion regulation is a key factor in relapse. It is not considered a first-line treatment for uncomplicated substance use disorder.

ACT is a form of applied behavior analysis (ABA) and grew from the same radical behaviorist perspective as ABA (Hayes 2004). The central components are cognitive diffusion (i.e., learning not to place a high importance on thoughts), acceptance of thoughts without judgment, and commitment to action based on one's core values.

Similarly, MBCT is a cognitive therapy that uses traditional cognitive therapy combined with mindfulness strategies. It has been primarily developed for the treatment of depression but has been used to address other mental health issues, including substance use disorder (Hoppes 2006).

48.2.2.7 CBT to Address Co-occurring Problems in AOD Treatment

Alcohol and other drug clients rarely present to treatment with *only* substance use disorders. Up to 80 % of clients seen in substance use treatment have co-occurring mental health issues (Mills et al. 2009), up to 80 % have been exposed to at least one traumatic event in their life with nearly half screening positive for some post-trauma symptoms (Dore et al. 2012), and an estimated 50–80 % have some level of functional cognitive impairment (Bates et al. 2002).

CBT is ideally suited to substance use treatment populations with comorbid disorders because it is highly structured, enabling those with cognitive deficits to gain benefit from the treatment, and has been well researched both in populations where these disorders are primary and in populations where these disorders co-occur with substance use problems.

48.2.3 Evidence to Support CBT

48.2.3.1 Traditional CBT Approaches

There is extensive evidence for the effectiveness of CBT for a range of mental health problems, including substance use disorders. McHugh et al. (2010) showed moderate effect sizes (on average $d = 0.45$) with the largest treatment effects found for cannabis use disorders, followed by cocaine, opioids, and then polysubstance dependence. Magill and Ray (2009) showed similar results.

The inconsistent use of the term "cognitive behavior therapy" to describe both interventions based on common general principles and specific treatments makes it difficult to distinguish outcomes between the different styles. However, overall, CBT appears to be both effective and long lasting when compared with general drug counseling, treatment as usual, and no treatment controls and is effective in both individual and group formats (McHugh et al. 2010).

A number of studies have examined specific relapse prevention treatments, including a systematic review of psychosocial interventions for substance use disorders (Dutra et al. 2008), which included five studies of RP that showed positive but modest outcomes on retention in treatment and substance use. Compared to other types of behavioral therapies, RP was most effective in maintaining abstinence post treatment (39 % abstinent post treatment), suggesting that if abstinence is the treatment goal, RP may be the treatment of choice.

Other treatments that draw heavily from the RP model have also been found to be effective. The matrix model (Rawson et al. 1995), for example, is a 16-week manualized group-focused outpatient intervention that includes many components of RP, plus a range of other behavioral interventions such as contingency management and 12-step participation. It has been found to be effective for a range of drug users, including amphetamine and cocaine users (Shoptaw et al. 2009).

In a review of CBT, RP, and contingency management, Dutra et al. (2008) found that the group referred to as "CBT therapies" (which included cognitive therapy and therapies drawn from CT such as dialectical behavior therapy) had lower dropout rates (35 %) than RP (57 %), equivalent effect sizes, but lower abstinence rates post treatment.

CBT appears to be more effective with the addition of contingency management, although the evidence is mixed and limited (McHugh et al. 2010). Project COMBINE (Anton et al. 2006) showed that in combination with medical management, "combined behavioral intervention" (including CBT) was as effective as naltrexone, and both were more effective than placebo for alcohol dependence.

48.2.3.2 Brief Therapy and Low-Intensity Interventions

A range of brief therapies have been developed and tested for a range of substance use disorders. Baker et al. (2005) trialed a brief two- and four-session treatment for methamphetamine users, drawn substantially from RP, and was found to be effective in increasing abstinence among severely dependent injecting methamphetamine users.

A five-session brief cognitive behavioral intervention improved confidence to resist urges in high-risk situations among heroin and methamphetamine users and a six-session brief intervention increased abstinence Yen et al. (2004); and sense of control over drug use and reduced drug-related problems among cannabis users (Copeland et al. 2001). Brief CBT interventions have also been shown to assist with cocaine, alcohol, and polydrug dependence (see Magill and Ray 2009 for a review) and with drug-related problems such as insomnia (Currie et al. 2004) and drug-related harms (Marlatt et al. 2012).

Low-intensity interventions have also been shown to be effective. A large international World Health Organization (WHO) study looked at screening

(using the AUDIT) and 5-min brief intervention in primary care (McAvoy et al. 2001). Computer-assisted CBT has been found to improve abstinence and treatment engagement compared to standard outpatient treatment for substance dependence (Kay-Lambkin et al. 2009) and for co-occurring mental health and substance use problems with some studies showing equivalent or better outcomes than treatment with a psychologist face-to-face.

48.2.3.3 Third Wave CBT Therapies

There is a more limited, but growing, research base for third wave, mindfulness-based therapies than other CBT interventions. Studies have shown reductions in substance use and craving and increases in acting with awareness and acceptance using mindfulness strategies (Bowen et al. 2009; Luoma et al. 2008).

Öst (2008) notes that the trial methods used in mindfulness-based studies have not been as stringent as that of traditional CBT so caution is required when comparing the two. A recent review of mindfulness-based therapies concluded that the data do not favor mindfulness-based interventions over traditional CBT interventions (Hofmann et al. 2010), with both showing similar effectiveness.

48.2.4 International Considerations

Cognitive behavior therapy has its origins in the developed world and is heavily based on Western concepts and models of illness (Rathod and Kingdon 2009). However, it is a broad and flexible model of care based on a well-grounded treatment formulation that can accommodate cultural and other influences and as a result has been adapted and successfully used across a number of cultures.

For example, in some cultures, such as many Indigenous groups, collective history is an important component of their world view (Rathod and Kingdon 2009) or, in CBT terms, their core beliefs. Although CBT does not tend to delve deeply into the past to routinely reappraise it, past issues are not precluded when they are driving or maintaining current problems, and CBT can easily accommodate these types of cultural differences.

Similarly, Hodges and Oei (2007) have examined the compatibility of CBT with Chinese values and have identified a number of potential issues for CBT, including the value Chinese and other Asian cultures place on conformity, certainty and discipline, persistence and a strong work ethic, and respect for authoritarian systems. In Asia more broadly, there is also a high level of stigma around mental health issues and a tendency for somatization (i.e., expressing mental health issues as physical symptoms).

Hodges and Oei (2007) argue that because CBT is structured and can be adapted to a more instructive rather than collaborative style, it may suit cultural contexts needing a directive and structured therapy style. This adaptation may suit the need for certainty and authority in these cultures and can also reduce the stigma of mental health treatment by using a more "coaching" style of therapy. Finally, they note that with the expansion of CBT using Eastern and Buddhist mindfulness strategies, CBT is well suited to Asian cultures.

CBT for mental health problems has been applied successfully in a range of diverse cultures and countries including, but not limited to, Pakistan (Rahman et al. 2008), Japan (Chen et al. 2007), and China (Williams et al. 2006) and among Latina women in the USA (Amaro et al. 2010), Muslims (Williams et al. 2006), and Aboriginal Australians (Laliberté et al. 2010), using a more narrative style of delivery sometimes referred to as "bush CBT" (Rickwood 2006). Although many of these studies are not specifically related to substance use disorders, the cross-cultural applications still apply.

48.3 Conclusion

CBT is an umbrella term that describes a wide range of therapies that have in common a focus on thoughts and beliefs as the central driver of, and the solution to, effective emotion regulation.

It tends to be relatively brief and highly collaborative. It is collaboration that is considered to be key in the development of the therapeutic alliance, an essential component of the application of CBT. It comes in a wide range of formats, including group and individual therapy, longer-term and brief therapy, and low-intensity interventions such as computerized CBT.

It is one of the most researched treatments in the world; both traditional (e.g., cognitive therapy) and newer (e.g., dialectical behavior therapy) models have shown effectiveness for treating substance use disorders.

Its structured and theoretical base makes it ideally suited to issues that co-occur with substance use problems, including common mental health problems, cognitive impairment, and trauma.

It has been adapted and applied across a range of cultures and countries. CBT is ideal for adaptation to non-Western cultures because of its flexible collaborative style and its reliance on effective case formulation.

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Psychodynamic Psychotherapy for the Treatment of Substance Use Disorders

49

Edward J. Khantzian

Contents

Abstract

An understanding of addiction to drugs and alcohol and their treatment is reviewed from a modern-day psychodynamic perspective drawing on ego/self-psychology and object relations and attachment theory. The author places emphasis on addictions as a self-regulation disorder. Deficits in regulating emotions, self-esteem, relationship, and self-care interact variably and cause individuals so affected to relieve their pain and suffering associated with these deficits with addictive substances and to become addicted to them. The author considers addictive drugs to be appealing not so much as pleasure producing but rather as agents that create and foster comfort and contact for individuals who are discomforted and disconnected. Alcohol and drugs relieve and/or change states of anhedonia, dysphoria, and unbearable painful emotional states. Individuals so affected discover that depending on the particular emotional pain with which they suffer, they discover a preference for a particular class of drugs. The action of each class of drugs is linked to how individuals discover these specific effects in relation to the suffering associated with their self-regulation problems.

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Appreciating these vulnerabilities and in contrast to outmoded psychoanalytic modes of detachment, passivity, and more strictly interpretive approaches, the author considers, from a contemporary perspective, important therapeutic elements and attitudes necessary to address the vulnerabilities such as being more interactive and to incorporate attitudes of kindness, support, empathy, respect, patience, and instruction in order to build and maintain a strong therapeutic alliance.

49.1 Introduction

Psychodynamic psychotherapy rests on the principle that important psychological factors are at the root of addictive behaviors and that these factors can be identified, targeted, and modified in the treatment relationship and thus eliminate or make less likely a reliance on addictive substances. We have reviewed elsewhere (Dodes and Khantzian 2005) early psychoanalytic formulations that, with a few exceptions, emphasized the use of addictive drugs as a regressive, pleasurable adaptation, whereas more contemporary formulations have placed emphasis on a progressive adaptation where addictive substances serve to cope with painful internal states and conditions and overwhelming external realities. Contemporary psychodynamic psychiatrists dating back to the 1960s and 1970s have reported on the nature of addictive vulnerability based on an appreciation of factors from structural, ego/self, and object relations perspectives. These perspectives underscore how disturbances and vulnerabilities in experiencing and processing emotions, sense of self/self-esteem, interpersonal relations, and behaviors are important if not essential factors for the development and maintenance of addiction to substance of abuse. Although there is empirical data supporting the efficacy of psychodynamic psychotherapy for a range of psychiatric disorders, including treatment of addictive disorders (Khantzian 2012; Dodes and Khantzian, in press; Shedler 2010), there is a rich clinical literature describing how an appreciation of the underlying dynamics of addictive behavior can be fathomed and targeted in individual and group therapy to help addicted individuals understand and modify these dynamics and overcome their addictive attachments and behaviors (Dodes and Khantzian, in press). Although individual psychotherapy is the primary focus here, this treatment modality should not or need not compete with complimentary or alternative treatments when psychodynamic findings indicate the need for additional or alternative treatment as will be discussed subsequently.

What is reviewed in this chapter derives mainly from clinical work with drug-dependent individuals. The chapter rests on the assumption that the case method and the treatment relationship (practice-based evidence) yields rich data that illuminates the nature of addictive disorders and provides keys to understand and treat patients who suffer with addictive illness. We will emphasize the more contemporary formulations that provide a basis to appreciate the vulnerabilities that underlie reliance on addictive substances and behaviors and how individual and group psychotherapy can ameliorate addictive suffering and modify addictive behavior.

49.2 Addiction as a Self-regulation Disorder

Addictive disorders are rooted in suffering – not pleasure-seeking or self-destructive motives as early psychodynamic formulations suggested. The suffering is mainly a consequence of addicted individual's inability to regulate their emotions, self-esteem, relationships, and behavior, especially their self-care (Khantzian 2012). From the earliest phases of infancy through early adult development, environmental influences around parenting, safety, comfort, traumatic abuse/neglect, and peer relationships are crucial in influencing self-regulation capacities, and significantly, experiences from earliest phases of development, for which there are no memories or symbolic representations, have some of the most profound influences (Gedo 1986; Khantzian 2003; Krystal 1988; Lichtenberg 1983). In this respect, these developmental factors weave their way through addictively prone individuals' ways of experiencing their emotions, sense of self, relationships, and behaviors to make addictions more likely. In what follows, I will elaborate on these self-regulation problems and how appreciation of the dynamics involved can guide effective individual and group therapeutic responses.

49.2.1 Disordered Emotions

Contemporary psychodynamic views have placed heavy emphasis on how addictively prone individuals suffer in the extreme with their emotions. Affect life at one extreme is perplexing, elusive, cut off, or absent, and at the other extreme feelings are overwhelming and unbearable. Terms such as alexithymia, disaffected, anhedonia, non-feeling states, etc., have been adopted to capture how feelings are not available, elusive, and disconnected, thus causing individuals so effected to feel empty, cut off, and unable to use their emotions to guide their reactions and behavior (Krystal 1988; McDougall 1984; Krystal and Raskin 1970). Krystal and Raskin (1970) appreciated some of the bases of these deficits when they described how feeling life has a normal developmental line (and potential for arrest or regression secondary to trauma or neglect) and how at the outset of life feelings are undifferentiated (i.e., anxiety cannot be distinguished from depression), that feelings are somatized, and without words (alexithymic). Addictively prone individuals at the other extreme suffer because feelings are intense, overwhelming, and unbearable. In this respect, more recent psychoanalytic investigators stressed defects in affect and drive defense and deficits in psychological structure to explain how substance-dependent individuals adopt addictive drugs to make intolerable feelings more bearable, especially those involving rage and aggression (Khantzian 1978; Weider and Kaplan 1969; Wurmser 1974).

These same investigators have elaborated on how addictive drugs can stimulate and enliven individuals who are cut off or feel vacuous or help to contain disorganizing and intense emotions when such affect is threatening or overwhelming. In these reports, the activating properties of stimulants and the releasing effects of low to moderate doses of depressants are described as correctives for individuals

experiencing their feelings as cut off or vacuous (Khantzian 1975, 1985, 1997). Weider and Kaplan (1969) coined the term "drug of choice," elaborating on how individuals self-select addictive drugs as a "prosthetic" to cope with overwhelming adolescent anxiety. The works of Wurmser (1974) and Khantzian (1985) emphasized the calming or muting action of opiates or obliterating doses of alcohol, especially for feelings of rage and aggression. What should be emphasized here is that these reports better focused on and appreciated how addictive drugs were used not for pleasure or self-destructive motives as early psychoanalytic studies stressed, but more precisely to selectively alleviate or make more tolerable affects that were confusing, unbearable, or intolerable.

More recently, Khantzian (2012) has considered some of the more subtle psychodynamics of addictive behavior that are insufficiently considered, namely, why so much of addictive behavior unfortunately continues to be linked to pleasure seeking (especially by neuroscientists) and how and why seeking relief from addictive drugs most usually produces more suffering than it relieves, and yet addicted individuals persist in the use of their drugs. In the former instance, especially those who are alexithymic and confused about their feelings, addicted individuals wittingly and unwittingly substitute the suffering which they perpetuate and control with use for the suffering they do not understand or control. The operative changes from simply relieving suffering, for one of control where they better understand and control it. In the second case, Khantzian (2012) has speculated, based on clinical observations, that addicted individuals often suffer with pervasive anhedonia and that the often magical relief they first experience with their drug of choice is experienced as euphoric, which is interpreted as pleasure, when in fact it is the result of relief of the anhedonia.

49.2.2 Disordered Relations with Self and Others

Dating back to the seminal contributions of self-psychologist Heinz Kohut (1971, 1977), recent formulations have underscored the faulty and troubled ways addictively inclined individuals suffer with troubled inner states of discomfort about self. Inner states of cohesion and well-being are lacking and lead to periodic and/or chronic feelings of helplessness, fragmentation, impoverishment, shame, and a low sense of self-worth; as a consequence, feelings of rage and defensive postures of omnipotence and bravado often result to mask underlying feelings of emptiness and inadequacy (Khantzian 2012). Dodes (1996, 2002) has emphasized how feelings of helplessness and compensatory narcissistic rage are major factors leading to drug use and relapse. On this basis, he formulated that addictions are a compulsive disorder and thus subject to traditional psychodynamic psychotherapy. Along similar lines, Director (2005) focused on feelings of powerlessness, unimportance, and compensatory reactions of omnipotence to explain recurrent relapse to addictive drugs in her work with two addicted women.

The importance of these perspectives is that clinicians must be sensitive and fine-tune to the troubled sense of self and painful lack of self-regard drug-dependent

individuals struggle with and to be appreciative of how the off-putting defensive characteristics can be understood as necessary postures to avoid narcissistic collapse. Furthermore, these findings indicate the significance of appreciating how such dynamics basically interweave with the compulsion to self-medicate the emotional pain such dynamics engender.

Troubled sense of self and self-esteem issues powerfully interact with relational difficulties for substance-dependent individuals. The early psychoanalytic literature linked addictions to pathological or problematic dependency. In contrast, contemporary psychodynamic views underscore problems of interpersonal isolation and counterdependence (Khantzian 2012). Although drug-dependent individuals suffer from enduring troubled, disrupted, and often traumatizing histories, experiencing or expressing their needs for connection and comfort with others that they so desperately need cannot be dared or accepted. As a consequence, feeling lonely, cut off, and alienated becomes a tragic way of life. Psychodynamic explorations of these attachment problems, more often infantile in origin, reveal how such adaptation is powerfully connected to addictive use of substance to deal with the associated distress and the pain perpetuating defenses of self-sufficiency, disavowal of need, and counterdependence (Flores 2004; Khantzian 2012; Walant 2002; Weegmann 2004).

Considering how these problems with sense of self, self-worth, and relational difficulties cause drug-dependent individuals so much pain and difficulty in tolerating distress and interactions with others, it should not be surprising the action of addictive drugs provide temporary relief and "solutions" to their intrapsychic and interpersonal pain and difficulties. Stimulants can counter states of helplessness, enfeeblement, and deflation in narcissistically injured individuals as well as provide a psychic boost for deflated self-esteem, or opiates can contain or offset the dysphoria that comes with disorganizing rage and make connections to others less threatening (Dodes 1996; Khantzian 1997, 2012). Low to moderate doses of alcohol can help shamefully restricted individuals, briefly, and therefore tolerably, to breakthrough and connect with others (Krystal and Raskin 1970).

These examples offer support for the recurrent clinical observation of why and how addictive substances become so compelling in individuals who suffer with an injured sense of self, poor self-esteem, and problematic interpersonal relations.

49.2.3 Disordered Self-care

Khantzian (2012) and Khantzian and Mack (1983) have described a fundamental ego function involved in life and in addictive vulnerability, namely, a capacity for self-care.[1] Self-care functions ensure safety, well-being, and survivability. They are underdeveloped or deficient in substance-dependent individuals. Early in his career, Khantzian (2012) cites his experience working with intravenous heroin users in

[1]The following sections on self-care and treatment are based in part on a recent report by Khantzian (2012).

a methadone program wherein he describes his powerful subjective reaction to the idea of injecting oneself with illicit drugs; he realized that his reaction of repugnance to that idea was one of countertransference (modern theorists would call it an "intersubjective" response, namely, patients getting the therapist to feel something that the patient is unaware or incapable of). Tactfully sharing his recoil and discomfort with the many patients he was evaluating consistently and monotonously elicited reactions of little or no emotions or concerns of alarm about crossing the so-called needle barrier. Subsequently, working with abstinent drug- or alcohol-dependent patients in psychotherapy, Khantzian was struck by how such lack of worry or thought persisted when no longer addicted. He observed these deficiencies to be involved in interpersonal and physical mishaps, slipups around management of important matters of unpaid premiums, lapsed licenses, and preventable medical and dental problems. It is in this context that he began to conclude that a major contributing factor to the development of addictions involved deficits in a capacity for self-care. Namely, addictively prone individuals think and feel differently about potential and real situations of harm and danger. Anxiety, fear, worry, and apprehension are deficient or absent and fail to guide such individuals in risky or self-harmful situations. There is a failure to draw cause/consequence relationship in the face of risk. Where anticipatory shame and guilt might guide when self-care capacities are better developed, in addictively prone people shame and guilt come after the fact (e.g., "I felt stupid and bad when I did that" [rather than] "I will feel stupid and bad if I do that"). It is the combination of self-care deficits interacting with the pain and suffering involved in self-regulation difficulties that makes vulnerable individuals more likely to develop addictive disorders.

49.3 Implications for Psychodynamic Psychotherapy

Treating clinicians need to constantly appreciate the underlying dynamics and vulnerabilities that govern addictive behavior. Considering the difficulties addicted individuals have with regulating their emotions, sense of self/self-esteem, relationships, and self-care, therapists need to think about therapeutic elements and attitudes that would best attune and respond to the suffering and dysfunction with which patients struggle. Old psychoanalytic approaches of passivity, therapeutic detachment, and strictly interpretive methods, therefore, would not be the order of the day. In fact, such approaches could perpetuate the confusion, shame, alienation, and disconnect with which addicted patients suffer. Thus, a contemporary psychotherapist needs to be more interactive (balance talking and listening) and incorporate attitudes of kindness, support, empathy, respect, patience, and instruction in the service of building and maintaining a strong treatment alliance. These elements are essential in order to deal with and overcome the problems with inaccessible or intense emotions, shame, broken self-esteem/relationships, and poor self-care (Khantzian 2012). Confrontation should be avoided and used only rarely such as concerns about safety but done in a way that preserves self-esteem.

The psychodynamic findings that have been outlined previously are considered in what follows, not only in reference to individual psychotherapy but also as they apply to considering other treatments, especially psychodynamic group therapy, as they can enhance individual therapy or be considered as alternatives when there are psychodynamic indications to do so.

Remembering how cut off addicted patients can be with their thoughts and feelings, therapists can help significantly with these dysfunctions by actively drawing out, identifying, and labeling feelings that begin to surface or seem evident to the therapist. When patients protest they do not know what they are feeling, treating clinicians should avoid concluding it is resistance or denial but rather use such interactions to invite and support the patient to consider the challenge of exploring, discovering, and understanding their feelings and emotions. Allen, Fonagy and Bateman (2008) have coined the term *mentalization* to emphasize one of the most basic aspects of psychotherapeutic work in general, but the concept preeminently applies to work with addicted patients, namely, to persistently focus on helping patients to access feelings, put them into words, and sustain them. Beyond individual therapy, the narrative and storytelling traditions that occur in group therapy and 12-step meetings are often very beneficial in helping patients to develop a capacity to recognize, express, and practice their own thoughts and feelings.

For those patients who struggle with and self-medicate intense and threatening emotions, particularly anger and rage, considerations and efforts should be made to help them contain and moderate the feelings that can feel so dangerous to self and others. It is worth noting how the positive treatment relationship and the therapist's concern for the safety of the patient is in and of itself a containing influence. For those whose rage and violent feeling derive from trauma and neglect, it is crucial to acknowledge and validate the legitimacy of such reactions and help them to understand how and why they have resorted to addictive drugs to contend with such intense emotions. Carefully timed and gentle explorations of the experiences that engender such emotions can gradually diminish or resolve such intense affect. In this context, judicious use of legitimate psychotropic medications targeting these affects can significantly attenuate the intensity to make the working through of these affects in psychotherapy more doable.

The support and empathy exhibited by the therapist in response to drug patients' pervasive sense of shame and broken self-esteem (predisposing and consequential) are a vital element in engaging and retaining such patients in psychotherapy. Such an approach helps in gaining inroads on the confusing and elusive ways in which the sense of self and others is experienced by substance users. Openings are created to focus on and help identify and resolve feelings of powerlessness, defensive rage, and reactions of omnipotence that are experienced and often surface in treatment. Patience, support, and kindness remain of paramount importance and allow for opportunities to therapeutically address and help the patient and the therapist, understand, and better work out problems with off-putting characteristics. These characteristics are more often reactive and defensive secondary to feelings of helplessness as well as feelings of unimportance (Dodes 1996; Director 2005).

And for those who are seemingly void of emotions and disengaged, the therapist may draw on their own energy and liveliness to help activate and enliven patients who are so affected. Again, group therapy experiences often can be invaluable in this respect in instilling and validating a better sense of self/self-esteem.

The issue of low self-esteem of substance abusers is related to their tendency to be avoidant of relationships and interpersonally isolated. They feel undeserving of the care and connection to others. Remaining interactive, engaging, and empathic are important elements in responding to patients' fear of and ambivalence about relationship. Impassivity and detached interpretations can be counter-therapeutic and devastating. Tactful focus on the ambivalence can materially stimulate possibilities of beneficial connections to others. It is in this respect that the connections stimulated by individual and group therapy are extraordinarily helpful in addressing and ameliorating the attachment difficulties and sense of alienation with which substance-dependent individuals struggle.

The thoughtless and unfeeling behaviors of substance-dependent patients that are characteristic of self-care deficits become manifest in the treatment relationship by the alarm stirred in the therapist by patients' risky or dangerous behaviors. Such reactions and interactions can alert the therapist and patient to how such deficits are major factors for patients to use and relapse to additive behaviors. The therapist should be unhesitant in using their reactions of alarm and concern that patients stir to identify the lack of such reaction in the patient. Constant attention to patients' poor self-care can help to instill a growing awareness of how their self-care deficits continuously leave those so affected continuously in harm's way, especially those involved with the harm and dangers associated with addictive substances. Long-term therapy often helps in getting at and understanding the developmental and environmental roots of these deficits, but a here-and-now, active, instructive approach is essential in order to stimulate and better develop a better capacity to recognize, anticipate, and avoid self-harm, particularly related to addictive substances. Finally, "We need to help patients use self-respect, feelings of apprehension/worry, relationships with others, and thoughtfulness as a guide for safe behavior and self-preservation" (Khantzian 2012, p. 278).

49.4 Conclusion

Contemporary psychoanalytic understanding of addictive disorders has generated and documented observable, developmental, structural, ego/self, and object relations disturbances that predispose to and maintain addictive behaviors and attachments. These findings provide a basis to identify the ways in which these disturbances affect feelings, self-esteem, relationships, and self-care. They provide a basis to guide therapists in targeting these problems psychotherapeutically. Impassive and strictly interpretive approaches are contraindicated if not damaging. Modern psychotherapeutic treatments employ more interactive, supportive, and empathic attitudes and techniques to help patients and therapist to focus on vulnerabilities and dysfunction that perpetuate addictive suffering and pain. This contemporary

perspective provides understanding, hope, and more effective means to overcome the compelling, self-defeating, and tragic causes and consequences of addictive disorders.

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Mindfulness as Behavioural Approach in Addiction Treatment

50

Marianne T. Marcus

Contents

Abstract

This chapter discusses the concept of mindfulness and reviews the theoretical and empirical evidence for the use of mindfulness-based strategies as behavioral approaches to addiction treatment. Mindfulness is defined as bringing nonjudgmental, intentional awareness to present-moment experiences. Mindfulness encourages the individual to acknowledge and accept thoughts, feelings, and bodily sensations as they arise, recognizing their impermanence. Mindfulness training as a component of addiction treatment is particularly compelling because it fosters acceptance of one's moment-to-moment thoughts and experiences rather than engaging in substance use to avoid or suppress distressing thoughts and emotions. Various psychological constructs associated with substance abuse, including experiential avoidance, stress, thought suppression, craving, self-compassion, and coping,

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have been studied in relation to mindfulness-based interventions for addictive disorders. Mindfulness-based behavioral interventions targeting these constructs, and addressing specific recovery populations, are explored. Those interventions include mindfulness-based stress reduction, mindfulness-based cognitive therapy, dialectical behavior therapy, acceptance and commitment therapy, mindfulness-based relapse prevention, mindfulness-based therapeutic community treatment, and mindfulness-oriented recovery enhancement. The intervention protocol, relevant mindfulness practices, and outcome measures studied for each of these treatment strategies are presented. The chapter concludes with a review of empirical evidence for mindfulness-based interventions for treatment of addictions and suggestions for future research.

Alcoholism is the disease of living elsewhere.
William Alexander (1997)

50.1 Introduction

Substance use disorders (SUDs) continue to be a public health problem across the globe. An estimated 230 million individuals, or 5 % of the adults across the world, had used an illicit drug in 2010. Twenty-seven million adults worldwide are estimated to be problem drug users (World Drug Report 2012). The World Health Organization reports that 2.5 million deaths result from harmful alcohol use each year, 320,000 of which are young people between the ages of 15 and 29 (WHO 2012). In the United States 58.3 million people aged 12 or older reported heavy drinking, 20.6 million were classified with substance dependence, and 68.2 million were current users of a tobacco product in 2011 (SAMSHA 2012). Substance use disorders are a major cause of disability and death worldwide. While the scope of SUD and the impact of the problem on health are incontrovertible, effective treatment and prevention of relapse pose challenges to researchers and clinicians. Addiction is defined as a chronic relapsing brain disease involving reward, motivation, memory, and related circuitry which leads to biological, psychological, social, and spiritual manifestations (ASAM 2012). Much has been learned about addiction and its underlying neurobiology over the past few decades. Addiction changes the brain causing characteristic behavior changes associated with enhanced motivational drive for the substance and weakening of control over this drive (Volkow et al. 2011). There has been increasing interest in the utility of mindfulness-based strategies in addressing the cognitive and emotional processes and behavioral urges underlying addiction (Dakwar and Levin 2009). The purpose of this chapter is to discuss mindfulness and review the theoretical and empirical evidence for use of mindfulness as a behavioral approach to addiction treatment.

50.1.1 Mindfulness

Mindfulness is defined as "paying attention in a particular way: on purpose, in the present moment, and nonjudgmentally" (Kabat-Zinn 1994). Mindfulness encourages awareness and acceptance of thoughts, feelings, and bodily sensations as they arise, recognizing their impermanence. Mindfulness teaches the individual to acknowledge and accept their experiences rather than to modify or suppress them. Mindfulness changes in one's relationship to present-moment experience have been described as "reperceiving" (Shapiro et al. 2006) or "attentional control," which may facilitate more mindful behavioral responses. The three axioms of mindfulness are posited to be *intention*, or the deliberate aspect of mindfulness; *attention*, or focus on the present moment; and *attitude*, or nonjudgmental acceptance (Shapiro et al. 2006). Mindfulness practice originated in the Buddhist tradition, but the associated set of skills can be taught independent of religious and cultural associations and in a variety of interventions (Baer and Krietemeyer 2006). Mindfulness-based approaches have been applied to a number of individuals and groups from those with physical or mental disorders to those who seek to reduce stress to improve general well-being (Baer and Krietemeyer 2006). Common elements in these approaches include focusing on whatever activity is at hand, whether it is breathing, walking, or eating, and observing the activity carefully. When the mind wanders the mindfulness practitioner is taught to bring the focus back to the target activity, observing and accepting the cognitions, sensations, or emotions that arise without judging or attempting to change them.

50.1.2 Mindfulness-Based Approaches to Substance Use Disorders

The utility of mindfulness training as a component of treatment for individuals in recovery from addictive disorders is particularly compelling. Mindfulness fosters an accepting attitude of one's moment-to-moment thoughts and experiences and might be expected to reduce the tendency to engage in substance use to avoid or suppress distressing thoughts and emotions. Various psychological constructs associated with substance abuse, including experiential avoidance, stress, thought suppression, craving, self-compassion, and coping, have been targeted in studies of mindfulness-based interventions for addictive disorders. Studies of mindfulness approaches as adjunct for particular treatment modalities such as therapeutic communities or relapse prevention programs are also increasing. Behavioral interventions which incorporate varying degrees of mindfulness training have been integrated into addiction treatment. Those interventions include mindfulness-based stress reduction (MBSR) (Kabat-Zinn 1990), mindfulness-based cognitive therapy (MBCT) (Segal et al. 2002), dialectical behavior therapy (DBT) (Linehan 1993), and acceptance and commitment therapy (ACT) (Hayes et al. 1999). Three recent modifications of these approaches were developed

specifically for substance-abusing populations, mindfulness-based relapse prevention (MBRP) (Witkiewitz et al. 2005), mindfulness-based therapeutic community treatment (MBTC) (Marcus et al. 2009), and mindfulness-oriented recovery enhancement (Garland et al. 2010). Descriptions of these approaches with examples of how they have been applied in the research literature are explored as follows.

50.1.3 Mindfulness-Based Stress Reduction

Mindfulness meditation is the foundation of the mindfulness-based stress reduction (MBSR) program developed by Kabat-Zinn in 1979 to teach patients with chronic physical and mental health problems how to improve their lives with a focus on reducing stress. Mindfulness meditation, derived from Buddhist *Vipassana* or insight meditation, is distinguished from *Samatha* or concentrative meditation techniques by its attentional style. Mindfulness meditation is a diffuse technique, allowing thoughts, feelings, and sensations to arise and experiencing them in a nonjudgmental, detached, and accepting manner. In contrast, concentrative meditation focuses on a single stimulus such as the breath or a mantra, excluding anything else (Dakwar and Levin 2009). MBSR was originally used as an adjunct to treatment in a wide range of chronic illnesses and as a psychosocial treatment approach to mental illnesses (Kabat-Zinn 1990, 2003; Reibel et al. 2001; Kabat-Zinn et al. 1992). Early studies indicate that MBSR was used to assist patients with psychosocial adaptation to chronic pain (Kabat-Zinn et al. 1986), depression (Teasdale et al. 2000); fibromyalgia (Kaplan et al. 1993), anxiety (Miller et al. 1995), and binge eating disorder (Kristeller and Halleh 1999). MBSR was also found to be a highly effective psychosocial approach for managing stress and mood disorder in cancer patients (Speca et al. 2000; Carlson et al. 2003). There is also evidence that MBSR is an effective stress reduction technique in nonclinical populations (Shapiro et al. 1998). MBSR is now being used as an adjunctive treatment for an increasing number of disorders (Ludwig and Kabat-Zinn 2008) including addiction. As originally developed, MBSR involves 8 weekly class sessions of 2 and a half to 3 h each. The teaching of MBSR is guided by a manual and includes a variety of mindfulness meditative exercises including breathing, sitting, walking, and eating. Hatha yoga postures are included as a way to cultivate awareness rather than as exercise. The body scan, or sequential focus on sensations in parts of the body, is also taught in MBSR. Classes are highly experiential with discussions of the various exercises as they occur. MBSR also includes homework. Participants are given audiotapes and encouraged to practice 45 min of formal, and 5–15 min of informal, mindfulness daily. Didactic information on stress is provided as well as a workbook to record weekly events associated with stress and mindfulness practice. The sixth class is an all-day experience of mindfulness, usually experienced in silence. Recommended guidelines for MBSR teachers are provided by the Center for Mindfulness at the University of Massachusetts Medical School where MBSR originated. Minimum qualifications include a master's degree in a mental health field, personal experience of daily meditation practice, attendance

at 2-week-long silent meditation retreats, 3 years' experience with hatha yoga, 2 years' experience teaching stress reduction, and attendance at a 5- or 7-day residential professional training program in MBSR (Baer and Krietemeyer 2006). Teacher certification is available through the Center for Mindfulness (Center for Mindfulness).

50.1.3.1 MBSR in Addiction Treatment

MBSR as described, with and without adaptation, has been studied in several addiction treatment approaches. Alterman et al. (2004) conducted a pilot study comparing outcomes of 18 randomized substance-dependent residents of a recovery house who received mindfulness meditation and standard treatment to 13 patients who received standard treatment alone. The only significant findings in this small study were changes in problem levels over time reported on the Addiction Severity Index (ASI) (McLellan et al. 1985). The ASI decreased in the mindfulness group, whereas it increased in the standard treatment alone group. The authors found that half of the MBSR group reported continued practice of mindfulness meditation 5 months after the baseline assessment which may indicate additional benefits from the intervention that were not captured by measures used in the study. Vidrine et al. (2009) conducted a randomized control pilot study to evaluate a mindfulness-based group therapy for nicotine dependence. Participants ($n = 158$) were randomly assigned to the mindfulness intervention or "standard of care." The 8 weekly MBSR sessions were integrated with a cognitive behavioral relapse prevention-based intervention consistent with a standard coping skills training approach (Fiore et al. 2000). This study found that mindfulness was negatively associated with the level of nicotine dependence and withdrawal severity and positively associated with a sense of agency related to cession, factors that have been found to be critical in assessing vulnerability to relapse.

50.1.4 Mindfulness-Based Cognitive Therapy (MBCT)

Mindfulness-based cognitive therapy (MBCT), which combines many of the components of MBSR with cognitive behavioral therapy (CBT), was designed to focus on depression and depressive relapses (Segal et al. 2002). The MBCT intervention is also taught in 2-h weekly class sessions for eight weeks in group format. Homework and group discussion are included but not a full day mindfulness session. MBCT differs from MBSR in the inclusion of a 3-min mini-meditation, or breathing space, which encourages focus on awareness of experiences for brief periods during the day to discourage automatic reactive behavior. During sitting meditation, MBCT practitioners are encouraged to think deliberately of difficult sensations or troubling problems, to face them, and work with them, rather than trying to avoid them. While MBCT does not include exercises to change thoughts traditionally taught in cognitive behavioral therapy, it does incorporate cognitive exercises related to thoughts, moods, and feelings. Participants are encouraged to develop relapse prevention action plans to implement when they experience

a negative mood. MBCT sessions are outlined in Segal et al. (2002). No formal set of qualifications have been proposed for MBCT therapists, but training in counseling, psychotherapy, or cognitive therapy is considered important (Baer and Krietemeyer 2006). MBCT has been found to decrease relapse of depressive disorders in several studies (Teasdale et al. 2000; Ma and Teasdale 2004; Teasdale and Ma 2004; Teasdale and Williams 2000).

50.1.4.1 MBCT in Addiction Treatment

Hides et al. (2010) conducted a systematic literature search to identify studies using CBT for the treatment of co-occurring depression and substance use. They found limited evidence for the effectiveness of CBT alone or in combination with antidepressant medication for the treatment of these comorbidities. They also concluded that while CBT was more efficacious than no treatment, there was little evidence that it is more efficacious than other psychotherapies for depression and substance abuse. They indicate that CBT may be enhanced for these disorders by combining it with other approaches such as mindfulness to induce a mediating or interacting effect on outcomes. Dakwar and Levin (2009) indicate that MBCT has not been evaluated for the treatment of substance abuse disorders alone, but there is interest in the theory, clinical application, and research of MBCT for mental health and SUD.

50.1.5 Dialectical Behavioral Therapy

Dialectical behavioral therapy (DBT) was originally developed for borderline personality disorder (BPD) (Linehan 1993), but it has been adapted for other conditions and comorbidities such as eating disorders, depression, and BPD with substance abuse (Dakwar and Levin 2009). The central dialectic in DBT is between acceptance and change, accepting the self while working toward change through skills training. The DBT treatment program incorporates an initial commitment to participate for a year, individual and group psychotherapy, shorter less formal exercises, and a cognitive behavioral component which includes four skill modules: core mindfulness, interpersonal effectiveness, emotion regulation, and distress tolerance. A manual is available to guide therapists of DBT (Linehan 1993). Therapist training for teaching DBT does not stipulate that the therapist have an ongoing formal mindfulness practice, but they must understand and be familiar with mindfulness and plan and practice the exercises in advance. Sharing and discussion of experiences is important in DBT as in MBSR and MBCT. A major point of discussion is the continued practice of mindfulness to confront the dialectical worldview emphasizing balance and synthesis of opposing ideas. DBT has been evaluated and found to be efficacious in reducing suicidal behavior and emotional problems in individuals with BPD (Neacsiu et al. 2010). A number of successful randomized control trials (RCTs) provide substantial supporting evidence for DBT as an efficacious treatment for BPD (Linehan et al. 2006; DeVylder 2010).

50.1.5.1 DBT in Addiction Treatment

For substance-dependent individuals DBT specifically targets behaviors that decrease abuse of substances, alleviate physical discomfort such as withdrawal, diminish urges and cravings, avoid cues to abuse, and increase reinforcement of healthy behaviors (Dimeff and Linehan 2008). The dialectic for the substance-dependent individual is to push for cessation of drug abuse (i.e., change) while accepting the possibility of relapse (i.e., acceptance) (Dimeff and Linehan 2008). Two RCTs have evaluated the efficacy of DBT for individuals with BPD and substance dependence. Linehan (1999) compared DBT with community treatment as usual among polysubstance-dependent women with BPD. Findings of the study indicate that individuals in the DBT group were significantly more likely to remain in treatment, achieved greater reductions in drug abuse, attended more individual therapy sessions, and sustained these outcomes at the 16-month follow-up assessment. In a second RCT with 23 opiate-dependent individuals, Linehan et al. (2002) compared DBT with comprehensive validation therapy plus 12 Steps (CVT + 12S), a manual-guided strategy that combines the major acceptance-based approaches in DBT with 12-Step participation. Both treatment conditions were associated with reductions in opiate abuse, but only the DBT participants retained those reductions during the last 4 months of treatment. The CVT + 12S intervention was more effective in retaining subjects to treatment. Subjects in both treatment conditions showed overall reductions in psychopathology levels from baseline and posttreatment and 16-month follow-up assessments.

50.1.6 Acceptance and Commitment Therapy

Acceptance and commitment therapy (ACT) is a behavioral and cognitive intervention which combines mindfulness and acceptance processes with commitment and behavioral change processes to induce psychological flexibility or the willingness to experience the present moment as it occurs (Hayes et al. 2011). A goal of ACT is to decrease experiential avoidance or the unwillingness to experience negative feelings, sensations, or urges and take action to eliminate those experiences. ACT strategies link behavior change to the individual's values, encouraging redirection and commitment to actions that are in line with those values (Hayes, et al. 2012). There is empirical evidence for the efficacy of ACT across a broad range of problems. A recent review by Ruiz (2010) reported 25 outcome studies (18 randomized trials) in clinical psychology, 27 (16 randomized trials) in health psychology, and 14 randomized studies in other areas including sports, stigma, organization, and learning. ACT is suggested as a unified model of behavior change applicable for major psychological problems as well as routine counseling to empower individuals to deal with social contexts (Hayes et al. 2012).

50.1.6.1 ACT in Addiction Treatment

Several studies illustrate application of ACT to addiction treatment. Smout et al. (2010) compared ACT with CBT in a randomized control trial for

methamphetamine use disorders ($N = 104$). Study participants were randomly assigned to 12 weekly 60-min individual sessions of CBT or ACT. Both interventions were guided by manuals adapted for the study. Doctoral- and master's-level therapists with experiential training in each intervention conducted the sessions. Therapy sessions were audiotaped and reviewed for adherence. The study found no significant differences between the groups in treatment attendance and methamphetamine-related outcomes. Both groups significantly improved over time on use, negative consequences, and dependence severity. The study authors suggest that ACT may be a promising alternative for treatment for methamphetamine use disorders. Vieten et al. (2010) developed and tested an acceptance-based coping intervention for alcohol dependence relapse prevention (ABCRP). The intervention combined elements from MBSR, MBCT, MBRP, and ACT. The first 3 months of the study were devoted to the development of a manual for the 8 weekly 2-h group-based sessions and a follow-up booster session to be administered 4 weeks later. The therapists were experienced in addiction treatment and the delivery of mindfulness-based interventions. The ABCRP intervention was administered to two consecutive cohorts of 22 participants in a local substance abuse treatment program, and participant feedback used to refine the manual. Adults over the age of 18 who were in their first 6 months of having quit drinking were then recruited to test the intervention. Pre- and post-data were collected on study completers ($N = 23$). Positive chances were reported in craving (decrease of 32 %; $P = .06$), positive affect (increase of 20 %; $P = .004$), negative affect (decrease of 32 %; $P = .0001$), emotional reactivity (decrease of 17 %; $P = .0001$), psychological well-being (increase of 15 %; $P = .004$), perceived stress (decrease of 23 %; $P = .002$), and mindfulness (increase of 21 %; $P = .002$). Mean percent days abstinent were 97.6 post intervention and 87.5 after 6 months, a change that was not statistically significant. These findings provide preliminary support for the clinical promise of ABCRP and the feasibility of adding acceptance-based coping in a mixed treatment for recovering alcoholics. Stotts et al. (2012) conducted a Stage I behavioral therapy trial of ACT for methadone detoxification. The goals of the study were to (1) decrease experiential avoidance and (2) make commitments to engage in value-based goals rather than allowing negative feelings and thoughts or withdrawal symptoms to influence behavior. Participants were opioid-dependent individuals currently taking methadone treatment at a licensed facility ($N = 56$). The study was a 24-week, randomized controlled parallel group pilot trial of two treatment conditions, an ACT-based opioid detoxification treatment or drug counseling. Both treatments were delivered in twenty-four 50-min weekly sessions. Both were guided by established protocols and audiotaped to assure adherence. No difference was found in opioid use during treatment, but 37 % of participants in the ACT group were successfully detoxified at the end of treatment compared to 19 % in the drug counseling protocol. Fear of withdrawal during detoxification was differentially reduced in the ACT group suggesting that ACT-based treatment has promise as an adjunct to detoxification in this population.

50.1.7 Addiction-Specific Mindfulness Treatment Approaches

50.1.7.1 Mindfulness-Based Relapse Prevention (MBRP)

Craving and negative affect are commonly endorsed risk factors for relapse, or the return to addictive behaviors after treatment (Witkiewitz et al. 2012; McMahon 2001). Marlatt and Gordon (1985) developed a cognitive behavioral relapse prevention program to teach skills such as identifying and coping with high-risk situations, triggers that threaten abstinence. MBPR combines mindfulness meditation practices with relapse prevention skills (Witkiewitz et al. 2012). Cognitive behavioral skills situations are taught with mindfulness practices to increase the participant's awareness and acceptance of challenging cognitive, emotional, and physical states. Unlike ACT and DBT in which mindfulness is one element of multicomponent therapies, mindfulness is the foundation of MBRP (Witkiewitz et al. 2012). MBRP, based on a manual, is taught in group format in weekly 2-h sessions. Each session includes formal guided meditation practice of 20–30 min. Participants are also introduced to experiential exercises which encourage nonjudgmental acceptance of negative thoughts and feelings rather than suppression of those potential cues to relapse. As an example, they are taught the SOBER space exercise as an alternative response to negative cues. The exercise teaches the participant to "stop," "observe," "breathe," "expand awareness," and "respond mindfully" to negative affective states rather than attempting to avoid them or change them (Witkiewitz et al. 2012). MBRP participants also receive meditation audiotapes and are assigned to practice daily (Chawla et al. 2010). Therapists who deliver MBSR in clinical trials typically hold master's degrees in psychology or social work and have a background in cognitive behavioral therapy and mindfulness meditation practice (Witkiewitz et al. 2013). Several studies have examined the effect of MBPR on client outcomes post treatment. Bowen et al. (2009) evaluated substance use outcomes in a randomly assigned group of inpatients and outpatients following an intensive stabilization period of treatment. Study participants ($N = 168$) were randomly assigned to an 8-week outpatient MBRP program or to treatment as usual (TAU), a 12-Step model with psychoeducational content. Findings indicate that consistent homework compliance, attendance, and client satisfaction support the feasibility of delivering MBRP in this setting. Significantly lower rates of substance use were reported in the MBRP group as compared to the TAU participants in the 4-month posttreatment period. MBRP participants also experienced greater decreases in craving and increases in acceptance and acting with awareness when compared to TAU participants. In a follow-up study Witkiewitz and Bowen (2010) examined the relation between depressive symptoms, craving, and substance use among the participants in the previous study. They found that craving mediated the relation between depressive symptoms and substance use among the TAU group but not the MBRP group. MBSR also attenuated the relation between posttreatment depressive symptoms and craving for 2 months following the intervention, a moderation effect which predicted substance use 4 months following the intervention. Witkiewitz et al. (2013) highlight the differing

perspectives on craving, biological, cognitive, and affective and suggest that a focus on all three may be important in understanding the impact of MBRP on craving. The authors stress that research which integrates information from brain to behavior is necessary to determine the various mechanisms of behavior change following mindfulness-based treatments such as MBRP (Witkiewitz et al. 2012).

50.1.7.2 Mindfulness-Based Therapeutic Community Treatment (MBTC)

Mindfulness-based therapeutic community treatment (MBTC) is an intervention designed to capture the congruence between the tenets of the therapeutic community (TC) method and the teachings of MBSR and to affect progress and retention in TC treatment through lowered stress. MBTC combines MBSR with the recovery curriculum offered in TCs, the "rules and tools of right living" (DeLeon 2000). Therapeutic communities (TCs) play an important role in the treatment of substance use disorders. TCs offer a unique approach to treatment, a highly structured social learning environment in which the community itself is the key element of behavior change. The major goal of the TC is to encourage and support social learning, which fosters changes in behavior and attitudes and the more elusive phenomenon of change in world view and self-image (DeLeon 2000). TCs hold that SUDs are disorders of the whole person which contribute to problems with socialization, cognitive and emotional skills, and psychological development. TCs stress living in the personal present and developing a positive work ethic, personal accountability, economic self-reliance, acceptance of family responsibility, community involvement, and concern for others (DeLeon 2000). Studies have shown that individuals who complete TC treatment have lower levels of substance use, criminal behavior, unemployment, and depression than they had prior to treatment (Simpson et al. 1997; Wexler et al. 1999) For individuals whose lives were characterized by impulsiveness and lack of self-control, the TC environment is restrictive and intrinsically stressful (Marcus 1998). TC dropout rate is significant, often as high as 50 %, with the highest attrition occurring the first 30–60 days after admission. A considerable body of research has shown that stress is associated with the initial acquisition of SUD behaviors in vulnerable individuals as well as with relapse or return to use following abstinence (Brown et al. 1995; Kreek and Koob 1998; Adinoff et al. 1998; Gordon 2002; Sinha 2001). MBTC includes the content and exercises taught in MBSR delivered in six longer sessions to coincide with the orientation phase of the TC. The didactic content is aligned with the TC teachings presented in orientation. Each session is illustrated with a corresponding principle of TC treatment. As an example, in Session l the MBSR protocol theme addresses reducing the tendency to operate on automatic pilot and stresses becoming awake. Session l of MBTC adds the TC principle that *right living* is being in the personal present, the here and now, and stresses that "to be awake is to be alive." The protocol and method are described in Marcus et al. (2007). Meditation practices include formal sitting, walking, the body scan, and mindful movement. Therapists are master's prepared in psychology or counseling, have a long-standing personal practice of mindfulness, and have completed the 7-day intensive training program

for health professionals offered by the Center for Mindfulness, University of Massachusetts Medical School. Further teacher preparation included 6 h of training on the TC method, a thorough orientation to the use of the manual, and a 6-week internship during which teachers observed and participated while an experienced, certified MBSR teacher taught initial sessions. A Stage 1 behavioral therapy trial of MBTC, using historical control methodology ($N = 459$), compared TAU ($N = 164$) with MBTC ($N = 295$) on measures of stress, the Symptoms of Stress Inventory (SOSI), and salivary cortisol in an 18-month residential TC. A survival analysis of time to dropout did not show a significant difference between the groups; however, the level of participation in MBTC was associated with decreased likelihood of dropout, and higher SOSI scores at baseline were associated with increased likelihood of dropout (Marcus et al. 2009). A linguistic analysis of written stories of stress from the historical control group ($N = 140$) and 253 MBTC participants was conducted to assess self-change. Data were collected five times over a 9-month period. Linguistic analysis showed no difference between the groups over time; however, over all time points, the MBTC group used fewer negative emotion words than the TAU group (Liehr et al. 2010). Three themes emerged from the content analysis of 38 written stories of stress conducted to formulate focus group questions to give voice to participants in the MBTC arm of the study. Participants identified three qualities of the experience: *utility*, or the usefulness of MBTC for calming the self; *portability*, or the potential for transferring MBTC lessons out of the classroom to real-life experiences; and *sustainability*, or the potential of MBTC to contribute to future goal attainment (Carroll et al. 2008). These studies provide support for further research on MBTC.

50.1.7.3 Mindfulness-Oriented Recovery Enhancement (MORE)

Mindfulness-oriented recovery enhancement (MORE) is a ten-session intervention for alcohol dependence which was adapted from mindfulness-based cognitive therapy, the mindfulness treatment developed to prevent depression relapse. MORE combines mindfulness meditation practices such as breathing and walking with addiction-specific experiential exercises to encourage participants to apply mindfulness principles to relapse triggers, craving, thought suppression, stress, and unconscious substance use behaviors (Garland et al. 2010). The MORE intervention, guided by a manual, was taught by a master's-prepared social worker who was trained in cognitive behavioral therapies and had mindfulness experience. Garland et al. (2010) compared MORE to an alcohol dependence support group (ASG) in a randomized controlled pilot study. The ASG intervention also included ten therapist-facilitated sessions in which participants were encouraged to discuss feelings and provide peer support but were not given prescriptive information for change. MORE participants were asked to practice mindfulness exercises for 15 min a day, while ASG participants were asked to journal on support group topics for 15 min per day. Study participants were 37 alcohol-dependent residents of an 18-month TC. Study outcomes revealed that MORE participants had significantly larger decreases in stress over the 10-week intervention period when compared to the ASG. The MORE participants also had significant decreases in

thought suppression, while the ASG participants increased thought suppression during the intervention period. Mindfulness training also increased physiological recovery from alcohol cues and modulated alcohol attentional bias, factors considered to be related to alcohol misuse (Garland et al. 2010). Eighteen members of the MORE group were interviewed in a subsequent qualitative to increase understanding of mindfulness-related treatment effects (Garland et al. 2012). Individual interviews of 15–30 min were conducted to ask open-ended questions about the MORE intervention, what participants liked, what could be improved, and how the experience benefitted the participant. A grounded theory approach and constant comparative methods were used in analyzing the interview data. Three general categories emerged: effects of the intervention on participant awareness, effects on coping, and participant perceptions of the most beneficial aspects of MORE. These findings provide further support for the therapeutic benefits of mindfulness training for individuals in recovery from alcohol dependence by eliciting their first-person experience which, in turn, informs and guides clinicians in providing the training.

Table 50.1 summarizes the major intervention models used in the studies of mindfulness-based approaches for SUD treatment. Most of the studies report adaptations of the original MBSR program developed by Kabat-Zinn (1990). The manner and degree to which mindfulness was integrated into the intervention was specified. Mindfulness content is foundational to MBSR, MBCT, MBRP, MBTC, and MORE, while ACT and DBT include only informal or brief mindfulness practices. Outcome measures relevant to initial recovery from substance abuse and prevention of relapse were collected across the studies.

50.2 Conclusion

While meditation practices were added to addiction treatment well over four decades ago, it was only in early 2000 that empirical reports of *mindfulness* meditation began to appear in the literature (Black 2012). Since that time there have been an increasing number of studies, and two systematic reviews, indicating the potential benefit of mindfulness approaches to the treatment of SUDs (Zgierska et al. 2009; Chiesa and Serretti 2013). Chiesa and Serretti (2014) note that the reasons why mindfulness may be of benefit to SUD treatment are related to the potential of mindfulness training to develop a nonjudgmental attitude toward distressing thoughts and feelings, adapt to one's own thought patterns, and accept present-moment experiences without attempting to suppress unpleasant experiences by using substances of abuse. These authors reviewed 24 quantitative, controlled studies of mindfulness-based or associated treatments for SUDs. The study interventions included MBSR, MBCT, MBRP, DBT, and ACT. Control conditions involved nonspecific educational support groups and wait-list controls. All four of the studies of smoking cessation reviewed showed significant benefits for the mindfulness condition over controls. While there was limited evidence that mindfulness interventions can reduce substance use over controls in studies of other substances such as alcohol, opiates, cannabis, methamphetamines, and

Table 50.1 Mindfulness approaches in addiction treatment

Intervention	Protocol	Mindfulness content	Outcome measures
Mindfulness-based stress reduction (MBSR)	8 weekly 2-h. classes, didactic information on stress, workbook	Variety of mindfulness meditative exercises, experiential discussion	Stress, addiction severity, level of dependence, withdrawal severity
	Therapist qualifications: master's degree, mindfulness experience, retreat attendance	Homework: 45 min. of formal and 15 min. of informal mindfulness practice daily guided by audiotape	
	Manual		
Mindfulness-based cognitive therapy (MBCT)	8 weekly 2-h. classes, didactic – cognitive therapy concepts without change concepts, relapse prevention action plans	Variety of meditative practices, 3-min mini-meditation	Co-occurring depression and substance use
	Therapist qualifications: training in counseling and cognitive therapy considered important		
	Manual		
Dialectical behavior therapy (DBT)	Individual and group psychotherapy	Core mindfulness module	Treatment retention, reduction in drug use
	Four skill modules: core mindfulness, interpersonal effectiveness, emotion regulation, distress tolerance central dialectic: acceptance and change		
	Therapist qualifications: must understand mindfulness and plan and practice exercises		
	Manual		
Acceptance and commitment therapy (ACT)	Behavioral and cognitive content to increase psychological flexibility, behaviors linked to values, varying length of sessions across studies	Mindfulness content directed at reducing experiential avoidance	Craving, negative affect, emotional reactivity, stress, positive affect, psychological well-being, mindfulness, successful detoxification
	Therapist qualifications: experience in addiction treatment and mindfulness-based interventions		
	Manual		

(*continued*)

Table 50.1 (continued)

Intervention	Protocol	Mindfulness content	Outcome measures
Mindfulness-based relapse prevention (MBRP)	8 weekly 2-h. sessions, guided mindfulness meditation with established cognitive behavioral program to teach skills to cope with relapse triggers, audiotapes, daily homework	Mindfulness is foundation, SOBER exercise (stop, observe, breathe, expand awareness, respond mindfully)	Substance use, craving, acceptance, acting with awareness
	Therapist qualifications: master's in psychology or social work, mindfulness practice, cognitive behavioral therapy training		
	Manual		
Mindfulness-based therapeutic community (MBTC)	6 weekly 3-h. group sessions, MBSR with social learning environment and therapeutic community curriculum, mindfulness homework	MBSR content aligned with therapeutic community curriculum, mediation practice room with audiotapes	Stress (salivary cortisol, psychometric measures, stress narratives), progress in therapeutic community, retention
	Therapist qualifications: master's preparation in psychology or counseling, long-standing personal practice of mindfulness, 6-h. training in therapeutic community method, 7-day mindfulness retreat		
	Manual		
Mindfulness-oriented recovery enhancement (MORE)	10 weekly group sessions combined MBCT with variety of mindfulness exercises, experiential discussion of application of mindfulness to relapse triggers, therapeutic community setting	Variety of mindfulness meditative exercises, 15 min of daily mindfulness practice	Thought suppression, stress, physiological recovery from alcohol cues, alcohol attention bias
	Therapist qualifications: master's-prepared social worker with mindfulness experience, trained in cognitive behavioral therapy		
	Manual		

polysubstances, methodological limitations were of concern. Those limitations included small sample size, lack of randomization, relative paucity of objective measures of drug use, and insufficient information on treatment adherence and follow-up. Zgierska et al. (2009) reviewed 22 studies, 13 of which were controlled, and concluded that while there is preliminary evidence of the efficacy of mindfulness interventions, significant methodological limitations exist in most of the studies. Despite study limitations noted in both systematic reviews, there is sufficient evidence to support future research in this promising area. In addition to larger trials and randomization, future studies should include refinements and more rigorous methodology. Recommendations include standardization of treatment manuals to facilitate data pooling and replication, assessment of participants' mindfulness practice or "dose," and appropriate controls including biomarkers (Zgierska et al. 2009). Neuroimaging offers another important avenue for exploring the effect of mindfulness-based interventions on addiction treatment. Neural correlates have been found on fMRI for individuals who have had as little as an 8-week course of mindfulness meditation (Farb et al. 2007) as well as for long-term practitioners (Short et al. 2010). Westbrook et al. (2013) examined the neural pathways linking a mindful attention exercise to reduced craving for cigarettes. Imaging results suggest that mindful attention decreases craving-related activity in the brain. Considering the promising early results of mindfulness-based interventions for treatment of addictions and recent advances in neuroimaging to investigate brain changes in addiction, it should now be possible to apply these techniques to fully understand how mindfulness practice may contribute to better outcomes for those who experience the devastating effects of addictions (Brewer et al. 2012).

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Contingency Management as Behavioural Approach in Addiction Treatment

51

John M. Roll and Bethany Fruci

Contents

Abstract

This chapter describes the underpinnings of the contingency management interventions for treating substance use disorders. It presents historical data establishing the efficacy of the procedures. Sections addressing key factors for the use of these protocols and current limitations are also included. In no way is the chapter meant to be an exhaustive review of the contingency management literature. Nor is the chapter intended to provide the necessary level of detail needed to implement these procedures. Instead, this chapter is a brief introduction to contingency management. Resources for implementation are included in the suggested reading section of this chapter. Contingency management interventions have shown remarkable promise for promoting the initiation of abstinence. The use of these protocols may increase overall treatment efficacy. The chapter is intended to introduce the reader to this class of interventions with the hope that they will be motivated to dig deeper into the extensive literature surrounding contingency management-based treatment of substance use disorders and associated comorbidities.

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51.1 Introduction

At its heart drug abuse – addiction – is an easy concept to understand. People misuse drugs because the drugs make them feel good. This occurs either by inducing euphoria or by eliminating an unpleasant state, for example, pain or withdrawal. The effects of drugs are usually short lived. That is to say that the euphoria or relief usually lasts for hours, not days. In order to regain the sought-after effect (feeling good), the drug must be taken again and again and again. This repeated consumption quickly turns into addiction. Addiction is a vicious cycle in which the original efficacy of the drug is diminished and must be taken more frequently and at higher doses to obtain similar efficacy (i.e., tolerance and habituation occur).

Addiction is often further characterized by damage to the physiology of the person consuming the drug as a result of the drug's pharmacologic action. The lifestyle associated with compulsive drug seeking also damages the person – they do not take care of their personal health, and their relationships with others deteriorate and often are terminated. Compulsive users often engage in dangerous behaviors to acquire drugs such as engaging in sex trade work or engaging in violent criminal activity. Unchecked, the person in the grasp of this vicious cycle of addiction will most often die or at best adopt what is essentially a palliative existence. This tragic outcome is the result of a person simply wanting to feel euphoric or seek relief from a negative state, something every human alive can relate to.

Characterizing this downward spiral that starts with the universal quest to feel good in terms of a scientific framework is important if we are to fully understand, effectively treat, and eventually prevent the condition. One of the best frameworks for characterizing addiction comes from the field of the experimental analysis of behavior. While this field has its genesis in the distinguished work of scholars such as the British philosophers Lloyd Morgan, Edward Thorndike, and others (e.g., Boakes 1984), it was essentially popularized and is most closely associated with the operant psychology of B. F. Skinner (e.g., Skinner 1938; See Roll 2014 for discussion of the history and evolution of operant psychology's influence on behavioral pharmacology).

One of the seminal events in the growth of operant psychology was the development of laboratory preparations (operant chamber, eponymously known as a Skinner box) for the convenient study of operant behavior. Briefly (see McSweeney and Murphy 2014 for a detailed discussion of operant psychology) organisms could be put into the operant chamber, and under tightly controlled conditions their behavior could be studied. A common example would be to place a hungry rat in the operant chamber and allow it to press a lever for food. Rate of responding for food will increase as the rat acquires the lever-pressing repertoire and then plateau as the rat masters the behavior. This change in rate across experimental sessions demonstrates learning. The food, which maintains the responding in the foregoing example, would be considered a reinforcer. A reinforcer can be defined as a stimulus that increases the behavior it follows.

In this case food reinforces lever pressing and the lever pressing increases until the behavior has been mastered. Most would consider the food to be an example of positive reinforcement. That is to say the behavior produces a stimulus (food) which increases the homeostatic "good" of the rat. Another type of reinforcement that can be demonstrated in a laboratory preparation is negative reinforcement. An example of this would be a rat placed in an operant chamber that receives a shock every 2 min regardless of what the rat did, in other words, the shock is inescapable. However, if a lever is placed in the box and the rat presses the lever, the next scheduled shock can be avoided. As in the positive reinforcement example, the rat will acquire the lever-pressing behavior over time until it has mastered the behavior and maintains it at a level that avoids shocks. Negative reinforcement, which is reinforcement that removes an aversive state, like this occurs when a behavior eliminates a noxious stimulus.

The forgoing is not merely a historical footnote. The use of the operant chamber opened many avenues for the study of how drugs influence behavior. Early examples of this work were conducted by Skinner and Heron (Skinner and Heron 1937) who examined how caffeine and amphetamine (Benzedrine) impacted food-reinforced behavior and the extinction of that behavior.

However, the aspect of operant psychology that is of the most relevance to this chapter was the demonstration that naïve animals would self-administer most of the same drugs abused by humans. In an early study, Thomson and Schuster demonstrated that drug-naïve monkeys would self-administer morphine (Thompson and Schuster 1964). This was a seminal demonstration that drugs of abuse could serve as positive reinforcers analogous to other positive reinforcers like food and water. Since this demonstration, thousands of studies in which drugs are provided to organisms (human and nonhuman) contingent on an operant response have demonstrated the robustness of this phenomenon (e.g., Roll 2014). It is one of the more unambiguous and well-accepted *facts* that drugs of abuse act as sources of positive reinforcement. Similarly, it has been demonstrated in laboratory paradigms that drugs of abuse can also serve as powerful sources of negative reinforcement (e.g., Holz and Gill 1975; Kandel and Schuster 1977; Thompson and Schuster 1968; Negus 2006; Negus and Banks 2013). In brief, drug-dependent organisms will increase their responding for a drug when they are in a state of withdrawal (see especially the body of work of Negus for discussion of this). That is, the animal, or person, will increase their consumption of a drug to escape from a negative state. In situations such as this, the drug may function as a negative reinforcer.

This observation that drugs of abuse serve as sources of reinforcement, both positive and negative, has been an important observation in our quest to understand, treat, and prevent addiction. Many would argue that the goal of treatment (and prevention) efforts should be the diminution of the reinforcing efficacy of the drug of abuse.

To relate this operant framework back to the opening discussion about a drug user's quest to feel good, we can refine that description so that instead of describing a quest to feel good, we can describe a quest for reinforcement. This could be

positive reinforcement, which some might equate with euphoria or negative reinforcement, for example, the diminution of withdrawal symptoms. This conceptualization now allows us to place drug addiction and its associated sequela into the operant psychology framework.

To appreciate the utility of this operant framework for addressing addiction, one more point needs consideration, that is, that primary, or naturalistic, reinforcers are biologically important for the survival of the organism and hence the species. Food, water, and sex are crucial to survival and these are powerful sources of natural reinforcement. Human biology has evolved to be maximally sensitive to sources of reinforcement such as these. A detailed discussion of the neurobiology underpinning reinforcement is well beyond the scope of this chapter. Suffice it to say that an impressive array of neurobiological systems are in play. When a thirsty person takes a drink of water, it is a powerful source of reinforcement, and our neurobiology guarantees that in a similar state of thirst, we will again seek a drink of water. Unfortunately, most drugs of abuse interact with the same neurobiological system that governs our reinforcing relationship to primary sources of reinforcement. As popularized by a past director of the National Institute on Drug Abuse, Dr. Alan Leshner, drugs of abuse hijack this neurobiological system and insidiously shift a user's motivation toward a compulsive focus on drug-derived reinforcement. The result is that an addicted person develops a compulsive motivation to seek drug-based reinforcement and that that reinforcement is of exceptional strength.

While daunting, this conceptualization does point toward an effective treatment mechanism. In order to help an individual enter into recovery from drug addiction, it is necessary to reduce the reinforcing efficacy of the drug. We would argue that this is the goal of all drug abuse treatment efforts at some level. The cognitive behavior treatments seek to restructure thoughts about drugs or to reorganize a user's cognitions so that they conceptualize the negative aspects of drug use as being more salient than the positive aspects. Motivational therapies seek to alter the user's motivation to seek the drug reinforcement; pharmacologic and immunotherapeutic approaches seek to block the drug from ever interacting with the user's reward-related neurobiology. While some will surely disagree, we postulate that all successful treatment approaches can be couched in terms of lowering the abused drug's reinforcing efficacy. One approach that takes this as its stated goal is contingency management (CM). The remainder of this chapter will focus on this approach. We will briefly describe the basic science supporting the approach and discuss prototypic examples of how to use the approach, key factors to consider when using the approach, populations for which the approach has been used, barriers to implementation, and finally potential limitations to the use of the approach. A series of meta-analyses supports the use of CM (Dutra et al. 2008; Lussier et al. 2006; Prendergast et al. 2006). The interested reader is encouraged to consult these publications as they are much more detailed than this chapter. There also exist a number of books on the topic of CM. We especially encourage the interested reader to consult those listed in Table 51.1. This brief chapter can provide only a glimpse of the wealth of research on CM. Consulting these other texts is crucial prior to actual implementation of the procedure.

Table 51.1 Suggested readings: complete references in reference section

Contingency management in substance abuse treatment – Higgins et al. (2008)
Contingency management for substance abuse treatment: a guide to implementing this evidence-based practice – Petry (2012)
Motivating behavior change among illicit-drug abusers – Higgins and Silverman (1999)
Reinforcement-based treatment for substance use disorders – Tuten et al. (2012)
Special issue on the behavior analysis and treatment of drug addiction, Journal of Applied Behavior Analysis – Silverman et al. (2008)

51.2 Contingency Management

51.2.1 Underlying Logic of CM Approaches

One of the clearest demonstrations of the underlying principle of CM-based interventions is found in a study by Nader and Woolverton (1991). In this study they allowed rhesus monkeys to make choices between intravenously delivered cocaine and food (Nader and Woolverton 1991). When the choice was between cocaine and a small amount of food, the monkeys showed a strong preference for self-administering the cocaine. However, when the dose of cocaine was held constant and the magnitude of the alternative source of reinforcement (food) was increased, the monkeys chose to self-administer cocaine on only about half of the choice opportunities. Finally, when the magnitude of the alternative reinforcer was increased even further, the monkeys selected the alternative reinforcer, food, almost exclusively. As discussed in Roll (2014), this well-designed experiment demonstrates the powerful impact of arranging an environment so that the organism needs to make choices between a drug and a salient, high-magnitude, alternative source of reinforcement. This finding has been demonstrated by many investigators working with different drugs, different alternative reinforcers, and different animal species (e.g., Carroll et al. 1989). When the magnitude of the alternative source of reinforcement is low, the drug has a powerful reinforcing efficacy. However, simply by elevating the magnitude of the available alternative sources of reinforcement, the reinforcing efficacy of the drug can be reduced to such a low level that it is not self-administered. That is to say, it is no longer an effective reinforcer.

It is reasonable to question how applicable these findings are to humans. In order to address this question, Higgins and colleagues conducted a similar study with human volunteers in which they investigated the impact of manipulating the magnitude of alternative reinforcers on cocaine self-administration (Higgins et al. 1994a). In this study, recreational cocaine users were recruited to participate in an outpatient study. Participants came to the laboratory where they made ten repeated choices between cocaine and money on a given day. Cocaine dose was 10 mg per choice and was held constant throughout the study. Money was used as an alternative source of reinforcement and was provided at three different levels: low, medium and high. During a given session monetary value was always held

constant. In each experimental session a participant made ten exclusive choices between cocaine and money. When the money value was low, participants elected to self-administer cocaine exclusively. As the value of the alternative source of reinforcement increased to a medium level, participants elected to receive about half of the available cocaine doses, and when the magnitude of the alternative was increased to a high level, participants switched their preference – relative to that demonstrated with the low magnitudes of alternative reinforcement – and elected to decline cocaine and receive only money. This procedure has been replicated with other types of drugs besides cocaine (e.g., Roll and Newton 2008; Roll et al. 2000). Exactly as in the Nader and Woolverton study with monkeys, the penchant for humans to self-administer drugs typically decreases in an orderly and predictable fashion as the amount of the alternative source of reinforcement increases. These data demonstrate that providing a salient alternative source of reinforcement of sufficient magnitude reduces a drug's reinforcing efficacy. As noted, we consider this to be the hallmark of the successful treatment of drug addiction. Contingency management approaches take advantage of this observation and seek to arrange a drug user's environment so that they can garner salient alternative sources of reinforcement when abstaining from drugs and forfeit that reinforcement when consuming drugs (note this section has been adapted from Roll 2014; also see Andrade and Petry 2014).

51.2.2 Prototypic Examples

Contingency management can take many forms, but in all cases it is a technique that clinicians use to *engineer* a drug user's environment so that the drug user must choose between drug use (maintained by the drug's reinforcing efficacy) and other nondrug reinforcers. The salient nondrug reinforcers that have often been employed included access to housing (Milby et al. 1996), access to employment (Silverman et al. 2012), provision of vouchers which can be exchanged for monetarily based goods and services (Higgins et al. 1994b), access to prizes which are valued by the user (e.g., Petry and Martin 2002), escape from judicial sanctions (Prendergast et al. 2008), and access to one's monetary resources (Ries et al. 2004). Several research groups have developed potential lists of other types of reinforcers that can be employed, and these include such things as reduced clinic fees, access to clinic-sponsored social events, fee rebates, and donated goods and services (e.g., Amass and Kamien 2008; Roll et al. 2005).

While the CM class of interventions have been used for most types of drug abuse treatment (Higgins et al. 2008), they have, in our opinion, been most successful for those types of addictions for which no viable pharmacotherapy exists. This largely excludes opioid addiction and nicotine addiction as both of these disorders can be controlled with pharmacotherapy (e.g., opioids: Bart 2012; nicotine: Aubin et al. 2013). That is not to say that CM cannot be a useful adjunct for the management of opiate addiction. For example, take-home doses of methadone that are delivered contingent on compliance with clinic regulations and the continued provision of

drug-free urine tests is a relatively common practice (e.g., Stitzer et al. 1992). Contingency management may also have utility in treating nicotine addiction (Ledgerwood 2008), but in our experience CM is usually a secondary focus to the pharmacotherapy, which is the first-line treatment of these disorders. Please note that even when good pharmacotherapy is available, some populations (such as pregnant women) may not be able to use the pharmacotherapy. In cases such as this, CM may become a very important treatment modality (e.g., Higgins et al. 2012. However, we still do not have accepted pharmacotherapies for psychostimulant addiction (excluding nicotine addiction), especially cocaine and methamphetamine. It is for these disorders that we believe CM is a useful first-line approach. There are two types of CM that are most commonly employed in the treatment of psychostimulant addiction. The first, popularized by Higgins (e.g., Higgins et al. 1994b), is perhaps best described as voucher-based reinforcement therapy (VBRT) and the second popularized by Petry (e.g., Petry and Martin 2002) is variously referred to as the fishbowl technique and prize-based CM, but is more accurately known as variable magnitude of reinforcement CM (e.g., Silverman et al. 2008). Examples of each are provided below, and in the following section the key factors related to the efficacy of the procedures are discussed.

Steve Higgins at the University of Vermont first demonstrated the efficacy of VBRT in a relatively large randomized clinical trial designed to assess the intervention's impact on cocaine-using individuals (Higgins et al. 1991). The basic procedures for this type of intervention are as follows: patients receive vouchers for the provision of biological samples (urine or breath) that indicate no recent drug use. Participants receive a voucher each time they test negative for the target drug. These vouchers can then be exchanged for goods or services. The initial voucher value is set at a low value (e.g., $2.50). Each consecutive instance of abstinence increases the magnitude of the voucher by a small amount (e.g., $1.50). Three consecutive abstinences result in the delivery of an additional bonus (e.g., $10.00). A drug-positive urine sample, or failure to test, results in a reset of the voucher magnitude back to its original level (i.e., $2.50), from which the escalation can begin again.

Nancy Petry at the University of Connecticut popularized the variable magnitude of reinforcement procedure (Petry et al. 2005). This procedure involves making "draws" from a bowl of chips representing different prize/reinforcer magnitudes. These chips can be exchanged for goods that are available on-site. Typically about half of the chips say "good job" and do not result in the delivery of any tangible reinforcement. 41.8 % of the chips result in a small reinforcer (worth about $1.00), 8 % result in a large reinforcer (worth about $20.00), and 0.2 % result in a jumbo reinforcer (worth about $80.00). Participants earn at least one draw for each urine sample submitted that is drug negative. The number of draws awarded at each urine collection escalates by with consecutive instances of drug-negative urine tests. Missing or drug-positive urine samples result in a reset to one draw available when the next negative sample is submitted.

Both of these (VBRT and variable magnitude of reinforcement) procedures are quite effective at treating psychostimulant addiction. In fact, the United States

Veterans' Administration has recently adopted CM as a treatment modality for psychostimulant addiction (Rash et al. 2013b). Often people wonder about the relative efficacy of the two procedures. It is important to note that there is substantial evidence suggesting that they both work. We are aware of no evidence demonstrating the superiority of one over the other. It is often erroneously claimed that the variable magnitude of reinforcement procedure is more cost-effective than the VBRT procedure. This is simply not true as the magnitude of the prizes or vouchers employed is scalable. That is, neither procedure has a universal inherent cost; the clinician can decide what the value of the prizes and the voucher will be (see below for a discussion of the importance of using relatively high-value reinforcement to insure efficacy in all CM procedures). Both procedures have the advantage that they allow clinicians and consumers of their services to celebrate success (e.g., drug abstinence) in a clinical session as opposed to focusing on failure (drug use). The variable magnitude of reinforcement procedure has a potential advantage in that the prize drawing phase has an inherent excitement built into and an element of chance which many may find exciting. This may confer additional reinforcing efficacy to the prizes above and beyond that which can be accounted for via their monetary value via a process of conditioning (e.g., Alessi et al. 2002). However, this suggestion is in need of empirical assessment. Some have suggested that on the face of it, this may resemble gambling and be a risk for pushing individuals who are seeking treatment for addiction to develop or exacerbate a pathological gambling problem. It is important to note that the variable magnitude of reinforcement procedure is not gambling. The participant does not put up any of their own resources and does not have an opportunity for personal financial loss as is the case in gambling. In addition, we have studied those going through this type of CM procedure and found no evidence that they transition to or develop a gambling disorder (Petry et al. 2006).

A potential advantage of the VBRT procedure relative to the variable magnitude of reinforcement procedure is that it allows a skillful clinician to engineer the voucher exchanges so that the consumer/patient comes into contact with powerful sources of nondrug reinforcement that exist in the consumer's natural environment. The hope being that these sources of naturally occurring reinforcement will come to exert control over the consumer's behavior as they initiate and maintain their recovery from their addiction, for example, exchanging vouchers for goods or services that allow the consumer to increase the reinforcement they get: from family interactions (e.g., exchanging a voucher so a mother can go roller skating with her daughter), from employment (e.g., exchanging a voucher for a set of clothes to wear at a job interview), or from engaging in a hobby (e.g., exchanging a voucher for a fishing license so that the consumer can engage in a hobby), all serve to increase the consumers contact with potentially powerful sources of nondrug reinforcement. In other words, the vouchers can act as behavioral vectors to draw the consumer's behavior into contact with nondrug reinforcers. It should be noted that in the variable magnitude of reinforcement procedure, this can also be accomplished by tailoring the prizes that are available to consumers.

In summary, both of these procedures work well and have improved the lives of many individuals who have benefited from treatment that utilized these approaches. There is no immediate reason to prefer one approach over the other. Both are effective if delivered with high degrees of fidelity. There is good evidence that the procedures work for most types of addiction (Dutra et al. 2008; Hartzler et al. 2012; Higgins and Silverman 1999; Lussier et al. 2006; Prendergast et al. 2006) and for many populations including adolescents (Branson et al. 2012), polysubstance abusers (Downey et al. 2000), pregnant women (Higgins et al. 2012), and those afflicted with both substance use disorders and serious and persistent mental health issues (McDonell et al. 2013). There is also evidence that the procedures work best for those who rapidly initiate abstinence during treatment (Yoon et al. 2009) and for those who begin treatment in a drug-free state (Stitzer et al. 2007). The utility of the CM procedures for treatment in the criminal justice system is less compelling (e.g., Hall et al. 2009; although see De Fulio et al. 2013). This is perhaps not surprising as most criminal justice systems are punishment based. While punishment is usually to be avoided in therapeutic contexts because of the proclivity of the person being punished to escape the punisher (e.g., terminate the treatment interaction), that is not an option in a criminal justice setting in which the person is compelled to engage in treatment. Given these circumstances contingent punishment should be quite effective in controlling behavior. For example, if a cocaine user is clearly informed that if they use cocaine they will be incarcerated, it is a powerful contingency management protocol based on punishment. This is the norm in many criminal justice systems (punishers range from mild sanction in some countries to death in others!). In such a milieu it is unlikely that a reinforcement-based CM procedure will garner much additional control over a user's behavior unless very high-magnitude reinforcers are employed. In criminal justice systems where behavior is less controlled, however, CM interventions should be effective.

51.2.3 Key Factors

In this section we briefly describe what we believe are four key factors for the successful implementation of any variety of CM. For a detailed discussion of these factors and others, please consult Petry (2012) and Tuten et al. (2012).

The first factor to consider is the procedure by which vouchers or prizes (henceforth both referred to as reinforcers) are disbursed. This is known in parlance of operant psychology as the schedule of reinforcement. Schedules of reinforcement have been extensively studied and it has been repeatedly demonstrated that schedule changes can have profound impacts on behavior (Ferster et al. 1957). Higgins developed the basic schedule that is routinely employed in CM procedures. This has two key components. First, as outlined in the examples in the previous section, there is an escalation in reinforcement magnitude for consecutive instances of abstinence. Secondly, as described above, there is a reset in reinforcer magnitude (voucher value or number of prize draws) following a failure to abstain. The combination of these components seems to provide the greatest likelihood for

achieving a successful treatment outcome (Roll et al. 1996; Roll and Higgins 2000). While we do not precisely know why these components are operative, it is likely that they function to integrate individual instances of abstinence into a consecutive period of abstinence. If each abstinence were reinforced independently of those that preceded or followed it, the behavioral target would be individual instances of abstinence. By linking consecutive instances of abstinence via the escalation and reset procedure, the target becomes consecutive instances of abstinence, which should be the goal of all treatment efforts. Whenever it is possible, CM procedures should try to incorporate both of these schedule components to have the greatest likelihood of success.

The second factor to consider is the magnitude, or value, of the reinforcers used. There exists an extensive body of literature from both laboratory and clinical trials and with different species, including humans, that unambiguously demonstrates that higher magnitudes of reinforcement are better at controlling behavior (Nader and Woolverton 1991; Packer et al. 2012; Wong et al. 2003). Clinically, this means that the higher the value of the reinforcer employed, the more effective it is likely to be. Use of reinforcer magnitudes that are too low to control behavior (e.g., Packer et al. 2012) will result in failure of the intervention. Unfortunately, this could be interpreted as a failure of the CM protocol, when in fact it is a lack of fidelity to the protocol that is responsible for the failure. One should not expect a low-magnitude reinforcer procedure to be very effective. This often poses a significant challenge to the implementation of CM (Roll et al. 2009). Treatment centers are often underresourced and do not have the means to employ high-magnitude monetary reinforcers such as vouchers and prizes. In this case, other noncash-based reinforcers can be used (as described above), or community donations can be sought (e.g., Amass and Kamien 2004). It is our belief that funders are beginning to embrace CM interventions as many insurance companies employ CM-based efforts to control health behaviors and as the United States Veterans' Administration adopts CM as a primary treatment strategy (Rash et al. 2013b). Hopefully, this will reduce the difficulty surrounding the provision of reinforcement of sufficient magnitude.

It should be noted that what is reinforcing for one person may not be reinforcing for another. Thus, when using noncash-based reinforcers, it is incumbent on the clinician to find reinforcers that are salient to individual consumers. This can be done by identifying a functional relationship between behavior and reinforcers as described in Johnston and Pennypacker (1993). Also of note is that reinforcement magnitude can be changed during treatment, if necessary, to garner more control over a user's behavior. In a study by Robles and colleagues (2000), it was demonstrated that even treatment-resistant cocaine users would abstain if relatively high-magnitude vouchers were used.

The third factor to consider when developing, or delivering, a CM protocol is delay (Petry 2000; Roll et al. 2000; Packer et al. 2012). There are two types of delay that are common in CM protocols. The first is the delay between earning a reinforcer (e.g., providing biological evidence of drug abstinence) and receiving the reinforcer, that is, how long after someone provides a drug-negative urine

sample until they receive their prize or voucher. In order to be maximally effective, this delay should be minimized. Another type of delay encountered when using vouchers is an exchange delay, that is, the delay between telling the counselor what you want to exchange your voucher for and the actual receipt of the item. Again, in order to maximize protocol efficacy, this delay should be minimized.

The fourth and final factor we wish to mention is intervention duration. While it is quite understandable that clinicians, consumers and their families, and funders want short, effective treatment, it is important to remember that addicts spend a lifetime developing an addiction; it may not be reasonable to think that the behavioral patterns established in order to support compulsive drug taking behavior can be terminated quickly. For this reason, we recommend that the longest possible duration of treatment be employed. There is evidence to suggest that longer treatments are more effective than shorter ones (Roll et al. 2013) and that long-term treatment is acceptable to consumers (Silverman et al. 2004).

51.2.4 Barriers

Given the widely accepted efficacy and relative ease of implementation, one could reasonably ask why CM is not more widely employed. To begin with, it is often employed although perhaps not as frequently as one would expect. In our experience, three common barriers are raised that hinder effective implementation of the procedure. These barriers have been discussed in detail and interested readers should consult the literature for a thorough vetting (e.g., Rash et al. 2012; Roll et al. 2009).

Primary among the barriers is the perceived cost of the CM interventions. We have touched on this in several of the above sections. Cost is an issue, but nonmonetary reinforcers can be employed. Some work has even demonstrated unanticipated benefits such as decreased hospitalizations and improved comorbid psychiatric functioning which result in significant cost savings (McDonell et al. 2013).

It has also been argued that CM protocols are too complex. Proponents of this argument claim that busy, poorly resourced clinicians do not have the time needed to calculate reinforcer value and carry out prize draws or voucher exchanges. While we certainly agree that clinicians are overworked and underpaid, we find this class of argument to be repugnant. It is akin to a surgeon declining to operate on someone because the surgical procedure was too complex and they were too busy with other procedures. Moreover, the advent of computerized programs to aid clinicians with the delivery of CM (www.bettertxoutcomes.org) and the ability to conduct online voucher exchanges (Meredith and Dallery 2013) obviate most of these concerns.

The final perception we wish to discuss is one of consumer resources. It has been suggested that CM-based interventions will only work for those who have limited financial resources. While it is undeniable that drug addiction eats away at a person's resources until they are depleted and that most abusers are financially

deprived, we are aware of no data to suggest that CM efficacy is influenced by income level. In fact, research has shown the income level (both legal and illegal) does not impact CM efficacy (Rash et al. 2013a). That said, most treatment efforts and especially those involving clinical research protocols for substance abuse are populated by individuals of limited financial means. Further work is needed to assess the efficacy of the monetarily based procedures in those of relative wealth. There is evidence that the use of nonmonetary CM is effective in those who have sufficient financial resource, however. Crowley and colleagues (Crowley 1984) demonstrated that attorneys and physicians who were abusing drugs could be treated by contingently arranging punishment. Crowley had the treatment seeking professionals write letters to their licensing boards which reported their substance addiction and requested that their license be revoked. Crowley kept the letters and did not mail them unless the professional tested positive for the prohibited drug in which case the letter was mailed. Evidence suggests that the procedure was effective.

51.2.4.1 Limitations

While we are strong proponents for the use of CM-based interventions, we are also realistic. As of yet there is no silver bullet for the treatment of psychostimulant addiction, including CM. In our experience, however, CM is a great treatment modality for initiating abstinence. While some have demonstrated encouraging long-term maintenance of abstinence post-CM-based treatment (e.g., Higgins et al. 2000), a perception lingers that long-term effects are difficult to demonstrate. As discussed above, we believe that VBRT provides a mechanism for bringing consumers in contact with nondrug sources of reinforcement than can serve to maintain abstinence, but in our experience this is not an automatic occurrence. Once individuals are treated for their addiction, they often find themselves right back in the same environment that occasioned their drug use in the first place. In this environment, the same pressures began to re-exert their influence and a risk of relapse is high. This brings us to our second limitation. We do not believe that CM should be a stand-alone intervention in most instances. Instead, we recommend pairing it with other evidence-based treatment. Drug abusers have complicated chaotic lives. They need help navigating affective, legal, and cognitive aspects of their addiction. While CM initiates abstinence and provides a sober client for the clinician to work with, it does nothing to inherently address these other concerns. These need to be addressed in the therapeutic relationship in order to maximize the likelihood of maintaining the abstinence which CM is so effective at initiating. One of the clearly most effective treatment strategies, the MATRIX model, does combine CM with other psychosocial modalities (Rawson et al. 2002).

51.3 Conclusion

An impressive array of basic science research supports the notion that drugs of abuse serve as potent reinforcers. Further, the hallmark of successful drug abuse

treatment is the diminution of the drug's reinforcing efficacy. CM is a very effective means for accomplishing this, especially in the treatment of psychostimulant addictions. Different types of CM appear to be generally effective and when delivered with high fidelity offer the clinician and the consumer perhaps their best chance for breaking the pernicious cycle of addiction.

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Twelve Step Facilitation as Behavioural Approach in Addiction Treatment

52

Dennis M. Donovan and Dennis C. Daley

Contents

Abstract

Hazardous and harmful alcohol use, illicit drug use, and the misuse of prescription medications represent major public health concerns that affect a large segment of the population. These highly prevalent conditions are associated with medical, social, and psychiatric comorbidities that bring them to the attention of practitioners in a variety of health-care and social service settings. While many such individuals will benefit from brief interventions or more formal specialty substance abuse treatment, many also might choose to engage in a mutual support program to seek assistance or gain additional support in their communities to help

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them achieve and maintain their goal of reducing or discontinuing their substance use. The present chapter reviews 12-step mutual support programs that serve as widely available, no-cost resources in substance abuse recovery. It reviews evidence about the effectiveness of such support groups and of specific interventions designed to facilitate engagement in them. It also describes the physician's role in educating patients and families in promoting 12-step programs. Important steps for physicians include understanding 12-step mutual support programs, preparing patients or family members to engage in a mutual support program, monitoring attendance and engagement, exploring patient resistances to mutual support programs, knowing the components and "tools" of the program, and being aware of alternatives for patients who will not use 12-step programs.

52.1 Introduction

Hazardous and harmful alcohol use, illicit drug use, and the misuse of prescription medications represent major public health concerns that affect a large segment of the population. These highly prevalent conditions are associated with medical, social, and psychiatric comorbidities that bring them to the attention of practitioners in a variety of health-care and social service settings (Kelly and McCrady 2008; Schulden et al. 2012). With an increased emphasis on conducting screening, brief intervention, and referral to treatment in primary care, emergency medicine, HIV and STI, and psychiatric clinics, the likelihood is high that medical and psychiatric practitioners will encounter individuals with substance use disorders (SUDs). While brief interventions in such settings may be sufficient to lead to behavior change for many, with a move toward either abstinence or reduced use and harm reduction, many other individuals will be referred for more intensive specialty substance use disorder treatment. Individuals might also choose to engage in a mutual support program to seek assistance or gain additional support in their communities to help them achieve and maintain their goal of reducing or discontinuing their substance use.

One such source of support is the large number mutual support programs based on the 12-step philosophy and principles, which originated with Alcoholics Anonymous (AA), but now includes Narcotics Anonymous (NA), Cocaine Anonymous (CA), and a number of others (Laudet 2008). These programs involve no cost and only require a desire to stop drinking or using drugs as a condition of membership, making them highly accessible and readily available, thus serving as important resources in substance abuse recovery. It is estimated that there are nearly 64,000 AA groups with 1.4 million members in the United States and Canada and over 114,000 groups and 2.1 million members worldwide (Alcoholics Anonymous 2012b). Similarly, NA and CA have meetings available throughout many countries internationally. All of these mutual support programs have also expanded their services through the availability of Internet-based meetings and "chat rooms" that provide an additional, supplemental source of support.

Given that many individuals who are in need of treatment never seek specialty SUD care, 12-step programs have served as the primary, if not only, source of

behavior change for many individuals dependent on alcohol or drugs. They have also been incorporated into specialty SUD treatment programs, either as a component of or as an adjunct to formal treatment, and have served as continuing care and community support following treatment. Of the over five million adolescents and adults in the United States that attended substance-focused mutual support groups during 2006 and 2007, approximately two-thirds were not involved in formal treatment during this period, while the remaining one-third were also involved in some type of specialty SUD treatment over that same period (Substance Abuse and Mental Health Services Administration 2008).

52.2 12-Step Approaches: An Overview

52.2.1 What Are 12-Step Programs?

Alcoholics Anonymous and other mutual support programs that are based on AA have their foundation in 12 steps, which represent a general philosophy, principles, beliefs, and behavioral guidelines for individuals seeking to discontinue their alcohol or drug use. The AA 12 steps are found in Table 52.1. The underlying philosophy reflected by these steps emphasizes a particular view of the recovery process. Acceptance of addiction as a disease that can be arrested but never eliminated, enhancing individual maturity and spiritual growth, minimizing self-centeredness, and providing help to other addicted individuals are all viewed as essential components (Humphreys et al. 2004). The 12 steps represent a series of self-reflective and behavioral activities that substance abusers engage in during their recovery. As noted in Table 52.1, individuals seeking to overcome their SUD should admit their powerlessness over alcohol and drugs, take a moral inventory of themselves, admit the nature of their wrongs, make a list of individuals whom they

Table 52.1 The 12 steps of Alcoholics Anonymous

1. We admitted we were powerless over alcohol – that our lives had become unmanageable
2. Came to believe that a power greater than ourselves could restore us to sanity
3. Made a decision to turn our will and our lives over to the care of God as we understood Him
4. Made a searching and fearless moral inventory of ourselves
5. Admitted to God, to ourselves, and to another human being the exact nature of our wrongs
6. Were entirely ready to have God remove all these defects of character
7. Humbly asked Him to remove our shortcomings
8. Made a list of all persons we had harmed, and became willing to make amends to them all
9. Made direct amends to such people wherever possible, except when to do so would injure them or others
10. Continued to take personal inventory and when we were wrong promptly admitted it
11. Sought through prayer and meditations to improve our conscious contact with God as we understood Him, praying only for knowledge of His will for us and the power to carry that out
12. Having had a spiritual awakening as the result of these steps, we tried to carry this message to alcoholics and to practice these principles in all our affairs

have harmed, and make amends to those people. The essence of recovery activities and guiding principles has been described as the 12-step "six pack": don't drink or use drugs, go to meetings, ask for help, get a sponsor, join a group, and get active (Caldwell and Cutter 1998).

In addition to the general philosophy and behavioral guidelines, 12-step approaches place a considerable emphasis on "fellowship" or the social network that is associated with 12-step group membership (Kaskutas et al. 2002). One of the characteristic features of a substance dependence syndrome is a narrowing of the drinking repertoire, which most often includes a narrowing of the friends and associates the individual has to those who are drinking/drug-using friends and acquaintances who tend to reinforce continued use. By joining a 12-step program, the individual begins to shift one's social network away from those who support drinking/drug use to an expanding network of those who support abstinence and promote recovery (Bond et al. 2003; Groh et al. 2008; Kelly et al. 2012, 2011; Longabaugh et al. 1998). There is an increased sense of bonding with other members in the fellowship who are also working toward a common goal of abstinence. This new social network provides a set of behavioral norms and role models for how to work toward abstinence and follow a personal recovery plan, the development and engagement in non-substance-related activities that are rewarding and can take the place of substance-related activities, a decreased exposure to drinking/drug-related activities and cues that induce craving, and rewarding social relationships (Kelly et al. 2011, 2012). Consistent with this, greater attendance at AA meetings was associated with decreases in social ties with individuals who supported the individuals' drinking and in drinking-related activities while also increasing social ties with those supporting abstinence and engaging in nondrinking activities, all of which contributed to better outcomes with respect to abstinence (Kelly et al. 2011). These social aspects of 12-step programs may be as important, if not more so, as 12-step specific factors or spiritual mechanisms in the positive benefits of 12-step mutual support groups (Groh et al. 2008; Kelly et al. 2012).

52.2.2 Effectiveness of 12-Step Programs

There is an increasing body of literature that indicates that involvement in 12-step programs is associated with both short-term and long-term benefits with respect to reduced alcohol or drug use and increased rates of abstinence, quality of life, and psychosocial function. In addition, engagement in 12-step programs is associated with reduced health-care, substance abuse, and mental health service utilization and costs (Humphreys and Moos 2001, 2007; Mundt et al. 2012).

The data supporting 12-step effectiveness comes from membership surveys, observational studies, and cross-lagged analyses of longitudinal studies. Surveys of AA and NA members indicate that the median length of abstinence among members is over 5 years, with approximately a third of each group having between 1 and 5 years of abstinence. Observational studies have demonstrated, for both alcohol- and drug-dependent individuals involved in and those not involved in

formal treatment, that increased attendance at 12-step meetings and involvement in 12-step activities and service have better outcomes across substance-related and psychosocial dimensions (Gossop et al. 2008; Humphreys 2003; Humphreys et al. 2004; Kaskutas 2009; Krentzman et al. 2010; Moos and Moos 2006; Pagano et al. 2013; Weiss et al. 2005; Zemore et al. 2013). It appears that both meeting attendance and engagement in recovery activities contribute to the observed benefit, with earlier, more frequent, and more regular attendance typically being associated with higher rates of abstinence (Zemore et al. 2013). This is consistent with 12-step programs' recommendation of attending 90 meetings in 90 days. While attendance trajectories that show low levels of attendance or an initial high level that subsequently drops off substantially most often are associated with poorer outcomes than patterns of high and consistent attendance or initially low but increasing attendance over time, many individuals who have limited attendance may also show benefit (Kaskutas et al. 2005, 2009a; Witbrodt et al. 2012). While even small amounts of participation may be helpful in increasing abstinence, higher "doses" (e.g., three or more meetings per week) may be needed to reduce the likelihood of relapse.

While attendance at meetings may decrease across time, the level of involvement in 12-step recovery and helping activities (e.g., doing service at meetings, reading 12-step literature, doing "step work," getting a sponsor, or calling other 12-step group members or one's sponsor, serving as a sponsor) may increase and that this engagement in such activities may be more important than meeting attendance (Owen et al. 2003; Pagano et al. 2013; Weiss et al. 2005). The results of longitudinal studies involving cross-lagged analyses or structural equation modeling have demonstrated that there is a causal pathway, rather than merely a correlational relationship, in which increased meeting attendance and/or engagement in 12-step activities leads to subsequent decreases in alcohol and drug use (Connors et al. 2001; Magura et al. 2013; McKellar et al. 2003; Weiss et al. 2005).

There have been questions raised about the applicability of these findings of benefit from 12-step involvement to particular subgroups of individuals such as women, minority groups, youth, and individuals with co-occurring substance use and psychiatric disorders. Although the literature has been somewhat mixed, it appears that these groups, despite potential barriers, do engage and can benefit equally from meeting attendance and engagement in 12-step activities (Donovan et al. 2013). In addition, many 12-step organizations have groups for special populations such as women, youth, and sexual minorities, and there are alternative groups available, such as Women For Sobriety, Double Trouble in Recovery, or Dual Recovery Anonymous, that may meet the specific needs of subgroups involved in the recovery process (Daley and McDonald 2013).

52.2.3 Interventions to Facilitate 12-Step Involvement in Specialty Treatment Programs

A number of interventions have been developed for use in substance abuse treatment programs to facilitate 12-step meeting attendance and engagement in 12-step

activities (Cloud and Kingree 2008; Donovan and Floyd 2008; Donovan et al. 2013). These differ with respect to their primary focus but share the common goal of getting individuals actively involved in 12-step groups. Twelve-Step Facilitation (TSF) therapy, developed in Project MATCH with alcohol-dependent individuals (Nowinski et al. 1992) and subsequently adapted for use with drug-dependent patients (Baker 1998; Carroll et al. 1998), focuses on helping individuals better understand and appreciate 12-step philosophy and the first three of the 12 steps, which focus on acceptance and surrender. The underlying assumption of TSF, which can be delivered in either individual or group formats, is that this increased appreciation will lead to subsequent engagement. Making AA Easier (MAAEZ) (Kaskutas et al. 2009b), a six-session group intervention, does not focus explicitly on 12-step philosophy and concepts. Rather, it attempts to facilitate 12-step engagement by familiarizing individuals with the "culture" of 12-step meetings, helping them identify potential barriers to engagement, and minimizing their resistance by helping them anticipate and learn ways to deal with issues in 12-step meetings and programs that often lead them to reject future participation. The intensive referral intervention (Timko and DeBenedetti 2007; Timko et al. 2006) focuses on a much more active and direct process of engaging individuals in meeting attendance. In a three-session, individually delivered intervention, an attempt is made to link the alcohol- or drug-dependent individual with a member of a community-based 12-step program who will accompany the individual to a 12-step meeting, thus helping reduce the potential fear of not knowing anyone at a meeting that can serve as a barrier to attendance. The volunteer helps prepare and "socialize" the patient, answering questions, introducing them to other group members, and serving as a transitional support. As with MAAEZ, the assumption of the intensive referral is that getting the individual to a meeting is paramount and that understanding of 12-step concepts and principles will follow. The STAGE-12 intervention (Stimulant Abuser Groups to Engage in 12 Step) (Daley et al. 2011; Donovan et al. 2012), consisting of three individual sessions and five group sessions, attempts to combine the active engagement process based on the intensive referral linkage with 12-step volunteers with TSF therapy content focused on better understanding 12-step concepts. The underlying assumption of STAGE-12 is that, given the high rates of early attrition, getting people to meetings may be insufficient to maintain involvement without an understanding of the philosophy and steps of the program; thus, a combined approach that focuses both on meeting attendance and active participation and on 12-step practices and principles may be needed. Each of these four interventions has demonstrated an ability to increase attendance and/or engagement in 12-step activities with a resultant decrease in alcohol or drug use.

52.2.4 The Physician's Role in Educating Patients and Families in Promoting 12-Step Programs

While such 12-step facilitative interventions in specialty treatment programs are effective, the majority of individuals with substance use disorders do not enter

specialty care. Approximately two-thirds of those who attended a mutual support program group meeting in the past year were not involved in some type of formal treatment over that same period (Substance Abuse and Mental Health Services Administration 2008). Many individuals with SUDs are seen in settings such as primary care, family practice, emergency medicine, or mental health settings, where there has been increased emphasis on screening, brief interventions, and referral to treatment. Many health professionals working in such non-specialty settings may be relatively unfamiliar with the general philosophy (e.g., the 12 steps and traditions) of 12-step-based mutual support groups in general, about the different types of meetings and the way in which they are conducted, about the benefits associated with participation in 12-step programs, and about recovery-oriented resources in their communities (Donovan et al. 2013; Kelly and McCrady 2008). Based on the evidence of the positive benefits associated with 12-step program involvement, the World Health Organization, in its advice concerning the management of alcohol use disorders, has recommended that nonspecialist health-care workers should routinely familiarize themselves with locally available mutual help groups and should encourage the alcohol-dependent patient to engage with such a group, should monitor the impact of attending the group on the patient, and should encourage family members of patients with alcohol dependence to engage with an appropriate mutual help group for families (World Health Organization 2012). The 2011 survey of AA members indicated that 40 % of members said they were referred to AA by a health-care professional and 75 % of members' doctors know they were in AA (Alcoholics Anonymous 2012a).

Physicians can assume many helpful roles with patients and their families vis-à-vis 12-step recovery programs. They can provide education, identify common resistances and help patients and families overcome these, facilitate their engagement in these programs, and monitor their attendance and involvement. Physicians who supervise, teach, or mentor medical students, residents, or other medical professionals can also prepare them for doing the same with patients in a broad range of settings from the emergency room to primary care practices to specialty practices (e.g., pain clinics, OB/GYN clinics, psychiatric clinics, etc.).

52.2.4.1 Understanding 12-Step Mutual Support Programs

The initial component of the World Health Organization's recommendation is to become familiar with local mutual support programs. A helpful strategy to learn about these programs is to attend meetings to "see" and "feel" the program in action. This makes it easier to explain the program to patients and family members. Attending "open" discussion and speaker meetings provides an experience that is valuable in knowing what occurs at meetings and how members help each other. We suggest attending meetings for patients with substance problems (Alcoholics Anonymous, Narcotics Anonymous, Cocaine Anonymous, or other 12-step programs) and for families affected by these problems (Al-Anon, Nar-Anon).

The physician can also encourage medical students, residents, and others involved in patient care to attend meetings and read literature (online or in written publications) describing these programs. Reading program literature can help the physician and medical staff understand these programs as well as serve as resources to recommend to patients interested in learning about and engaging in these programs (Alcoholics Anonymous 2001, 2009; Narcotics Anonymous 1993, 2008). Alcoholics Anonymous has developed a special brochure and video to help familiarize physicians and health-care providers about the program and ways to facilitate referrals to it (Alcoholics Anonymous 1992).

Following are some key issues in understanding 12-step programs and facilitating their use by patients or their family members:

- These programs consist of many components: meetings, the 12 steps of recovery, sponsorship, recovery slogans, recovery literature, supportive activities (e.g., holiday events, conventions, sober social events), and service.
- Meetings are free and accessible in many countries and communities and follow a similar format, depending on the type of meeting (open or closed; speaker or discussion meeting). Attending different meetings can help the patient find ones that fit his or her recovery needs.
- No one is in charge of the 12-step fellowship and all members are equal. Discussion meetings have chairpersons to lead discussions, but these are members of the program. Meetings are "anonymous" and no records are kept.
- People from all walks of life can attend, even if they are not yet abstinent from alcohol or drugs. The only requirement is a "desire to stop" using alcohol or drugs.
- Members become educated about addiction, recovery, and other topics/issues. Some may even learn social and/or recovery skills such as how to self-disclose (cravings, problems, feelings, and thoughts) and to accept or give support.
- The emphasis of 12-step programs is one alcoholic or drug-addicted individual helping another. Newcomers are welcomed and accepted, which helps reduce their shame. Program members help them learn to work a "we" versus an "I" program.
- Members help each other by sharing their experience with addiction and recovery, thereby sharing hope and strength. This is done at the meetings, at "meetings after the meeting" (e.g., members go out for tea or coffee after a meeting to support each other in recovery), and via sponsorship.
- Members who connect with others can reduce their isolation. They can receive social support and help from other members "who have been there" and are managing the common challenges faced in recovery from alcoholism or drug addiction.
- Groups and other program activities are a positive replacement for drinking or drug use. In early recovery, addicted patients often struggle with boredom and not knowing what to do with their time. Some lack non-substance leisure interests.
- Group members can give participants (especially newcomers) a "dose" of reality to reduce their distorted or "stinking" thinking as well as recovery sabotaging

behaviors such as missing meetings, not showing a commitment to the program, or failure to get "active" in using the tools of the program.
- Members also help each other get back on track if one has a lapse or relapse. Members are encouraged to use these experiences to change their recovery program.
- These programs are spiritually based, not religious. Many members find it helpful to identify a power greater than oneself. For those who do not believe in God or a supreme being, the 12-step fellowship can serve this role of something "greater than the self."

52.2.4.2 Preparing Patients or Family Members to Engage in a Mutual Support Program

Physicians and medical staff can educate patients or family members about these programs and discuss their resistances, concerns or questions, and prior experiences. The care provider can recommend specific types of programs or meetings. This can be done in brief face-to-face interactions during the medical visit as well as by providing written literature or giving information about how and where to get literature about these programs. For example, in response to a patient's comment "I don't like to share my personal business with strangers," the physician can respond "I can understand why you think that way Mrs. Brown. You are not required to share anything you do not want to talk about at meetings. One option would be to attend a speaker's meeting at first where you hear others in recovery share their stories. Later, you can consider discussion meetings where you can talk about your drinking, too."

Or, in response to a family member who says "my husband is addicted to cocaine and ruining our family," the physician may respond "Mrs. Johnson, I can hear your distress about your husband's cocaine use. I recommend counseling to help you deal with this. We will provide you with names of counselors or clinics. I also want to tell you about a support program called Nar-Anon that helps family members cope with the distress caused by a loved one's drug addiction. Some of my other patients have told me how Nar-Anon has helped them learn to deal with their family member's drug problem. They also say this helps them focus on their own needs as well and not put all their energy on the addicted family member."

Physicians and medical practices can provide information on bulletin boards in the waiting or examination rooms and give patients or family members local meeting lists, brochures (e.g., "*This is AA*; *Frequently Asked Questions about AA*; and *Is AA for You*?"), or handouts with telephone numbers they can call to get this information from local AA, NA, Al-Anon, or Nar-Anon offices. Having names and phone numbers of volunteers active in mutual support programs to offer to patients or family members can also facilitate a patient's transition to meeting attendance. This, however, requires relationships with individuals in recovery who are trustworthy and have a natural desire to help patients or families deal with substance-related problems. Programs using such peer volunteers have been particularly successful (Blondell et al. 2001a, b), often even more so than direct physician encouragement and referral (Manning et al. 2012). The *Bridging the Gap* program

of Alcoholics Anonymous, which uses volunteers in recovery to help facilitate the transition of alcohol-dependent individuals from treatment programs into community-based 12-step programs, may be a resource (Alcoholics Anonymous 1991) and could be contacted through the local AA office. However, due to HIPPA regulations, physicians would have to get patients to agree to initiate the contact with a community volunteer rather than provide a patient name to a volunteer.

52.2.4.3 Monitoring Attendance and Engagement

Another strategy is briefly inquiring about the patient's current involvement in mutual support programs. This can help the care provider get a sense of what the patient is learning and gaining from the program. Or, it can help to identify problems that interfere with their ongoing attendance or participation. For example, Dr. George said to one of her patients who she referred to AA "to give me a brief update on how your AA program is coming along." When the patient responded "well Doc, I found the meetings helpful, but I've been busy and have been missing them lately," her physician explored the details of this and found that "lately" was the past 3 months. Dr. George was then able to help the patient recognize stopping meetings as a potential relapse risk factor. She also got this patient to commit to resume regular AA attendance. This process worked out well as the patient did not relapse and returned to regular AA involvement.

In another case, a patient complained about some of the people he described as "shady" at a NA speaker meeting that attracted a large number of people. The patient believed some of these people were not serious in the program and had questionable intentions, which made him uncomfortable. After a brief discussion, his physician got the patient to agree to connect with others at this meeting who he believed were serious or to attend other NA meetings. The patient learned from this experience that he had to decide who to connect with at the meetings and how to deal with unpleasant issues that may arise such as members with questionable motivation.

52.2.4.4 Exploring Patient Resistances to Mutual Support Programs

Resistances are common among individuals new to 12-step programs as well as among some regular attendees. Some common resistances stated by patients include "I don't like to open up with strangers, the program is too religious for me, some people who go are hypocrites because they go out after the meeting and drink (or use drugs), I don't like being told what to do by someone else, or I'm different that 'those' people." A good strategy is to do what proponents of Motivational Interviewing refer to as "roll with the resistance." Let the patient share his or her concern and then reflect this back in an empathic, nonjudgmental manner in which the patient is not told what to do. "Mr. Kelly, I appreciate you telling me that you worry about sharing personal information with strangers. That's understandable since you are a private person. Some of my other patients who expressed this concern tell me that starting out with speaker meetings instead of discussion meetings helped ease them into the program because they did not have to share any details of their past. Later, when they felt more

comfortable to attend discussion meetings, sharing was easier for them. What do you think about this idea?"

52.2.4.5 Knowing the Components and "Tools" of the Program

Health-care providers can use their knowledge to educate patients and deal with their concerns and questions about mutual support programs. They can also help patients find "specialty programs or meetings" to help meet their needs related to a personal characteristic or situation (e.g., a physician; a young person; a gay, lesbian, bisexual, or transgender patient; or one with an addiction and a psychiatric illness). A brief summary of components and program tools is given as follows (Daley and Donovan 2007):

- **Meetings**, which usually last 1 h, are either "open" or "closed." Open meetings are for anyone who is interested in the particular 12-step program and can be attended by students, professionals, and other nonmembers interested in learning more about the recovery programs. This is the type of meeting that physicians and other health-care providers can attend to familiarize themselves with the programs. Closed meetings are limited to members and prospective members only. There are two primary types of closed meetings: (a) a speaker meeting in which a member shares a personal story of addiction and recovery, which is known as a lead or a qualification, and (b) a discussion meeting in which members share ideas and experiences related to a specific topic (e.g., gratitude, relapse, acceptance) or one of the 12 steps or 12 traditions. The provider can recommend a patient new to the program to try a dozen meetings before judging their helpfulness. Also, have meeting lists available for patients and families or know where they can obtain these.
- **Chat rooms or online resources**, many of which are available 24 h a day. These include chat rooms for those with addiction as well as family members or significant others, including adult children of alcoholics (ACOA) or drug-dependent parents. See AA, NA, Al-Anon, or Nar-Anon websites to access their chat rooms, or go to other websites such as www.aalivechat.com or www.nachatroom.org or use an Internet search engine and enter "AA, Al-Anon, NA, Nar-Anon, ACOA chat rooms or online meetings." These online resources are viewed as ways to supplement, not replace, attending meetings in person.
- **Sponsorship** refers to a member in the program with substantial recovery who mentors new members in a variety of ways (attending meetings together, talking by phone, meeting outside of meetings, working the 12 steps, providing support and feedback, and facilitating the use of the tools of the program). Sponsors have been found to serve three broadly defined functions in their relationship to the individual: (1) encouraging the new member to become actively involved in 12-step activities, (2) providing ongoing emotional, social, and personal support, and (3) sharing their own personal experience of recovery through which they serve as role models (Whelan et al. 2009). Not only does sponsorship benefit the new 12-step member, it also helps to solidify the sponsor's own recovery through the principles of "giving back" (Pagano et al. 2004, 2010).

- **Higher Power** refers to "something greater than oneself" to help in the recovery journey. Many of the 12 steps (steps 2, 3, 5, 6, 7, 12) focus on spirituality and how to use a Higher Power to deal with the challenges of recovery. However, for those who do not believe in God as a Higher Power, the fellowship of AA or NA can be the suggested source of an "outside" support to the patient.
- **12 steps of AA, NA, or other programs** provide a way to actively engage in the recovery journey by understanding the spiritual principles of the program. The 12 steps focus on the following: (a) acceptance of addiction and negative effects on life (e.g., powerlessness and unmanageability), (b) spirituality (e.g., relying on a "Higher Power"), (c) self-assessment (e.g., looking at one's character defects and strengths via a personal inventory), (d) making amends to loved ones and others hurt by one's addiction, and (e) service by carrying the message of the program to others with alcoholism or drug addiction.
- **Slogans** refer to sayings or ways of thinking to help the member think more like a person in recovery and less like an addicted person. These can be used to coach oneself through stressful times such as when the member has a strong craving for alcohol or drugs or is obsessed about using. Some of the more common sayings include "One day at a time," "easy does it," "this too [craving/desire] shall pass," "let go and let God," and "put off the first drink (or drug)," to name a few.
- **Providing or recommending literature** about these programs or common issues faced by members is a helpful intervention. AA has the "Big Book" and NA has the "Basic Text," as well as many other books and information pamphlets or tapes on addiction or recovery. AA, NA, Al-Anon, Nar-Anon, and other 12-step programs all have a rich selection of recovery literature for all phases of recovery. Many members continue to use this literature on a daily basis years (or even decades) into their recovery.
- **Events** sponsored by these programs include those that take place during the holidays to provide extra support during high-risk times for some members (e.g., Christmas and New Year), as well as social events such as picnics or attending some activity of mutual interest (e.g., bowling or a sports event). In addition, there are a number of Alano Clubs and Recovery Cafes found in many cities. These venues, in addition to hosting recovery group meetings, provide alcohol- and drug-free environments in which recovering individuals and their families can engage in social and recreational activities. These activities reinforce the belief that is possible to have fun without being under the influence of alcohol or drugs.

52.2.4.6 Alternatives for Patients Who Will Not Use 12-Step Programs

It is not unusual for some patients to state that they have tried 12-step programs to no avail, they are simply not interested, or they have difficulties accepting the basic philosophy and spirituality of the programs. If, after exploring the resistances to find out what did not help or any other experiences that impacted on not wanting to use program, the physician believes an alternative mutual support approach could help, then options for non-12-step programs can be provided. These include, but are not limited to, the following: Women for Sobriety, Men for Recovery, Rational Recovery, SMART Recovery, Secular Organizations for Sobriety/Save Our Selves

or SOS, and others. One potential limitation is that these groups are less readily available than are 12-step groups, with many towns or cities having few or none of these programs available.

52.3 Conclusion

Mutual support programs (12-step and others) are an excellent resource for individuals with alcohol or drug addictions as well as loved ones or significant others adversely affected by an addiction. These programs are available at no cost, and each provides a framework for recovery, based on the philosophy of the program. The most widely used and available programs are AA, NA, An-Anon, and Nar-Anon. Becoming familiar with these programs, educating patients about them, providing literature or meeting lists, facilitating attendance, and monitoring involvement are some of the helpful strategies for physicians and their medical staffs to help patients with alcohol and drug problems and affected family members.

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Group Therapy for Substance Use Disorders

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Contents

Abstract

Group therapy is the predominant type of behavioral therapy offered in substance use disorder treatment settings. This chapter provides an overview of the research literature on the efficacy of group therapy for substance use disorders

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and discusses research challenges and important future directions in the study of group therapy. Research on the efficacy of group therapy for substance use disorders has generally found that it is associated with superior outcomes compared to no treatment or treatment as usual. Studies examining the combination of group therapy with other forms of treatment, such as pharmacotherapy, have been mixed, with some studies finding additive benefits and others finding no benefit. However, group therapy appears to be equally as effective as individual therapy and may offer cost benefits relative to individual treatment. Group therapy for co-occurring substance use disorders and other psychiatric disorders, such as bipolar disorder and posttraumatic stress disorder, is associated with benefits for both disorders. Due to a number of difficulties with conducting research on group therapy, this treatment modality remains understudied compared to individual therapy. Additional research is needed to identify the most effective types of group therapy and its optimal delivery method, either alone or in combination with other therapies.

53.1 Introduction

The term "group therapy" encompasses a number of treatment approaches that share in common the presence of at least two independent (i.e., not related) patients and a therapist who conduct meetings with the goal of eliminating or reducing substance use or substance use disorder (SUD) symptoms (Weiss et al. 2004). Specific treatments falling under this umbrella term may emphasize the interactions among members and the therapist (process or supportive therapy groups), the provision of information and skills (psychoeducational or behavioral therapy groups), or both. The content of groups also varies and may include components such as psychoeducation, cognitive-behavioral or motivational interventions, "check-ins" about use and other symptoms, encouragement to attend 12-step or other mutual help groups, relational interventions, skills training, and contingency management, among others.

The vast majority of programs that specialize in treating SUDs report offering some form of group therapy (more than 94 %; United States Department of Health and Human Services 2010). The predominance of group therapy in these settings may be attributable – at least in part – to the potential cost savings of a group rather than an individual approach. Cost analyses have suggested that group therapy is associated with substantially less therapist time per patient compared to individual therapy (Sobell et al. 2009) and that it has both the lowest cost and best cost-effectiveness ratio of psychosocial treatment approaches (French et al. 2008). In addition, patients are generally satisfied with group therapy as indicated by similar (if not superior) retention rates compared to individual therapy and strong self-ratings of treatment satisfaction (e.g., Sobell et al. 2009). Studies of patient preference for group versus individual therapy are few; however, at least one study has identified preference for group therapy over individual therapy (Schmitz et al. 1994). Thus, group therapy appears to be a highly acceptable and low-cost approach to treating SUDs.

Despite the widespread use of group therapy, this approach has been studied far less extensively than individual therapies. In this review, we aim to characterize the current research on the use of group therapy for patients with SUDs, with a focus on randomized controlled trials. We will limit our definition of group therapy to treatments that focus on substance use or associated symptoms and not on treatments targeted specifically to other symptoms or co-occurring disorders (e.g., group cognitive-behavioral therapy for depression in patients with SUDs). Where possible, we will attempt to characterize the nature of the group therapy approach from a content (e.g., cognitive-behavioral, psychoeducational, etc.), composition (e.g., targeted substance, single or mixed gender, dual diagnosis), and timing (e.g., acute care, aftercare) perspective. We conclude with a commentary on limitations and challenges in conducting research on group therapy and an integration of findings from the literature to date.

53.2 Efficacy and Effectiveness of Group Therapy

53.2.1 Is Group Therapy Effective for the Treatment of SUDs?

Although the majority of group therapy studies have compared two (or more) types of group therapy, several studies have attempted to answer the basic question of whether group therapy leads to improvement in SUD symptoms. These studies compare either treatment as usual (usual care at a facility) to treatment as usual plus group therapy or group therapy to no group therapy.

53.2.1.1 Comparing Group Therapy to Usual Care or No Group Therapy

Studies of the effect of group therapy on SUD outcomes in general have suggested that group therapy is effective in reducing substance use and associated impairment. Stephens and colleagues (2000) randomly assigned 291 treatment-seeking marijuana users to 14 sessions of group cognitive-behavioral therapy, two sessions of individual motivational treatment, or a waitlist control. Participants in both active treatment groups reported significantly greater reductions in marijuana use and consequences of use than the waitlist control group throughout treatment and 16 months of follow-up. Group therapy and brief individual therapy were not significantly different on any outcomes. In a similar study, two sessions of group therapy were significantly more effective for reducing nicotine use in undergraduate smokers compared to a waitlist control group (Omer et al. 1998).

However, not all studies have yielded positive results. In a study of interventions to prevent relapse among abstinent smokers following 3 months of treatment with group therapy and/or nicotine replacement therapy, participants were randomly assigned to receive one of two counseling groups or no group treatment (Razavi et al. 1999). Abstinence rates were not significantly different across conditions after 12 months (range from 50 % to 58 %), suggesting that adding group counseling as a relapse prevention strategy after acute treatment was not beneficial for increasing abstinence rates.

53.2.1.2 Adding Group Therapy to Pharmacotherapy

Because pharmacotherapy is a first-line treatment for dependence on some substances of abuse (e.g., heroin, nicotine), a number of trials have tested whether adding group therapy to medication can enhance outcomes. A trial of adding 12 sessions of group cognitive-behavioral therapy to the opioid antagonist naltrexone for opioid-dependent individuals found no difference between those who received group therapy and those who received naltrexone alone (Tucker et al. 2004). However, it is important to note in this study that fewer than 10 % of the group therapy condition participants attended all group sessions. Moreover, participants in both conditions were permitted to engage in additional psychotherapy (including individual), with more than 85 % of participants electing to do so. Thus, it is unclear whether the results reflect a failure of group therapy, an underdosing of group therapy, or an effect of adjunctive treatment that was received by both groups (e.g., individual therapy).

Luthar and colleagues conducted two studies examining a relational psychotherapy group for heroin-dependent mothers (Luthar and Suchman 2000; Luthar et al. 2007). This relational intervention used a supportive orientation focused on enhancing women's functioning and parenting. A study comparing this approach to methadone maintenance treatment as usual (including group counseling and case management) in 61 heroin-dependent mothers (Luthar and Suchman 2000) found modest benefits of relational therapy for some parenting measures (e.g., risk of child maltreatment, affective interactions), but not others (e.g., limit setting, instrumental behaviors). Modest benefits were seen for depressive symptoms at posttreatment; however, this was no longer significant at follow-up. The relational group was associated with greater opioid abstinence, but not cocaine abstinence. This treatment was then examined in a larger study of 127 heroin-dependent mothers receiving methadone maintenance compared to methadone maintenance plus a recovery training group therapy focused on psychoeducation and skills training (Luthar et al. 2007). Although the relational therapy was associated with some benefits at posttreatment, many of these benefits were reversed over a 6-month follow-up, with the comparison condition associated with better functional and child maltreatment outcomes.

Studies of the addition of group therapy to medication for nicotine dependence have yielded mixed results. In a study of 154 nicotine-dependent women randomized to receive combinations of bupropion or placebo along with either cognitive-behavioral or supportive group therapy, a complex and mixed set of results emerged (Schmitz et al. 2007). Specifically, cognitive-behavioral therapy resulted in significantly higher abstinence rates than did supportive therapy among those taking bupropion. However, supportive therapy was associated with superior outcomes among participants receiving placebo. The combination of bupropion and cognitive-behavioral therapy did not result in better abstinence rates compared to either placebo condition (Schmitz et al. 2007).

A study by Smith and colleagues (2001) randomized 677 smokers following an initial brief treatment (nicotine replacement therapy and one session of individual counseling) to six sessions of cognitive-behavioral group therapy, a motivational enhancement/supportive group therapy, or no group therapy; all participants also

continued to receive nicotine replacement therapy. There were no significant differences among the three treatment conditions in terms of self-reported cigarette use; however, smokers who had not achieved abstinence during the initial treatment period had better outcomes in the motivational/supportive treatment relative to the cognitive-behavioral or no group conditions.

Overall, group therapy for SUDs appears to be superior to either waitlist or no treatment. Studies examining group therapy as an aftercare strategy or as added to pharmacotherapy are more mixed. In these studies, results imply that the effects of treatment may vary based on the subgroups (e.g., adding group therapy as aftercare may be effective for initial treatment nonresponders; Smith et al. 2001). Additionally, mixed patterns of results regarding combination group therapy with pharmacotherapy imply that certain therapies may better complement certain medications; however, additional studies are needed to understand whether such interactions exist and can be used to maximize outcomes.

53.2.2 Is Group Therapy as Good as Individual Therapy?

Several studies have tested whether the same type of treatment is more effective when delivered in a group or individual format. The largest well-controlled study of this association was conducted by Sobell and colleagues (2009) in a sample of 264 individuals with "non-severe" alcohol and drug use problems (those with a history of severe dependence were excluded). Participants were randomly assigned to four sessions of a cognitive-behavioral or motivational intervention in a group or individual format. Participants experienced significant reductions in self-reported alcohol and drug use and consequences of substance use. Results also indicated no differences in substance use outcomes for individual versus group administration for either alcohol or drug use and no differences in treatment retention.

In another study of group versus individual delivery of a motivational therapy, John and colleagues (2003) randomized 343 alcohol-dependent inpatients in German psychiatric hospitals to receive either three sessions of individual therapy or nine sessions of group therapy for enhancing motivation for alcohol abstinence following detoxification. Those in the group therapy condition reported more self-help group attendance; however, there were no differences in other forms of treatment-seeking and overall service utilization between groups. There were also no differences in alcohol outcomes between these groups, with fewer than 30 % in each group reporting abstinence at 6 months after detoxification.

Studies comparing individual and group cognitive-behavioral therapy have yielded similar results. A study of the use of 9 weeks (12 sessions) of cognitive-behavioral relapse prevention in group or individual format for 47 cocaine-dependent patients following inpatient treatment found similar outcomes for both groups over time on rates of abstinence as well as drug-related problems and measures of functioning (Schmitz et al. 1997). By the end of treatment, fewer than 50 % of both groups had remained abstinent, although gains in functioning and impairment were largely sustained over 24 weeks of follow-up; at the final

assessment point, the average days of cocaine use in the previous month were low (2 days for individual and less than 1 day for group).

A similar study also compared individual to group relapse prevention as part of an aftercare program for 132 patients with alcohol and drug dependence (Graham et al. 1996). Patients received 12 weekly sessions of either 45–60 min individual or 60–90 min group therapy. Group and individual therapy had similar outcomes for treatment adherence and retention and self-reported alcohol and drug use. However, group therapy was associated with better social support at 12-month follow-up. A study conducted in Brazil randomized 155 mixed alcohol- and drug-dependent patients to receive 17 sessions of cognitive-behavioral therapy in either group or individual format (Marques and Formigoni 2001). This study also found no significant differences in session attendance or in self-reported alcohol or drug use outcomes between groups when controlling for baseline levels of use.

A Norwegian study tested 12 weeks of 90-min group therapy (with same-gender composition) or 7 h of individual delivery of a short-term therapy based on social learning theory, focusing on skill acquisition toward individualized treatment goals (abstinence or harm reduction) (Duckert et al. 1992). Study participants who responded to advertisements and reported "alcohol problems" were randomized to one of these conditions and followed for 21 months. Although there was a higher rate of abstinence among women in individual therapy at the 3-month follow-up, there were no differences between groups at any subsequent time throughout the follow-up period. At the end of 21 months, almost 70 % had reduced their alcohol consumption from pretreatment levels and half of the total sample reduced alcohol use by at least 50 %.

Although relatively few studies have specifically tested individual versus group therapies using the same group content, the available research very clearly suggests that individual and group therapies are generally equivalent in terms of both retention and clinical outcomes. Thus, it seems that high-quality treatment can be administered as effectively in group as in individually delivered formats.

53.2.3 What Types of Group Therapy Are Most Effective?

The majority of studies examining group therapy for SUDs have focused on comparing two or more types of group therapy that vary in terms of content or approach. For example, several studies have compared skills training to other interventions and have yielded mixed results. Eriksen et al. (1986) randomized 24 alcohol-dependent participants to eight sessions of social skills training or counseling. The social skills training group reported fewer drinking days, drank less alcohol overall, and had better employment outcomes. A comparison of coping skills and interactional (interpersonal) groups for alcohol use disorders found no overall differences between the conditions in terms of alcohol use; however, individuals rated high on psychopathy had better outcomes with the coping skills group and those low on psychopathy had better outcomes in the interactional group, both following treatment (Kadden et al. 1989) and at 2-year follow-up (Cooney et al. 1991). A later study by this group randomized 250 alcohol-dependent patients

to either a random treatment assignment or matched treatment assignment based on level of psychopathy (Kadden et al. 2001). Results of this study were mixed, with higher rates of abstinence in the randomized condition, but fewer alcohol-related consequences in the matched condition.

Several studies have compared cognitive-behavioral therapies to other therapies or control conditions. Kaminer et al. (2002) randomized 88 adolescents presenting for outpatient substance abuse treatment to receive either cognitive-behavioral or psychoeducational group therapy. Results suggested an early benefit for cognitive-behavioral therapy; however, this was moderated by gender and age (with younger males responding better to cognitive-behavioral therapy) and the benefits were not maintained at 6-month follow-up. Both groups exhibited similar changes in substance use and functioning over time (Kaminer et al. 2002).

Similarly mixed results were found by Pomerleau et al. (1978) in a study of 32 alcohol-dependent men comparing behavioral therapy to psychodynamic group therapy. Results indicated better retention and less alcohol use in the behavioral therapy condition (consisting of several behavioral interventions, such as stimulus control and shaping), but higher rates of abstinence among completers of the psychodynamic therapy. A later study of male alcohol-dependent patients in a Veterans Administration hospital found no differences between cognitive-behavioral and interpersonal therapies on alcohol use outcomes (Ito et al. 1988). A study comparing 6 weeks of 12-step counseling (usual care) to behavioral skills training therapy, transactional analysis therapy, or their combination (Olson et al. 1981) found that all conditions were associated with superior outcomes compared to transactional analysis alone.

A comparison of six sessions of cognitive-behavioral group therapy for smoking cessation compared to a health education control plus nicotine replacement therapy in a sample of 154 African American smokers found greater rates of abstinence (past week) among those in the cognitive-behavioral therapy condition through 6 months of follow-up, with 31 % versus 14 % of participants abstinent at the end of follow-up (Webb et al. 2010).

Telch et al. (1984) compared supportive therapy, behavioral therapy (covert sensitization), and a control therapy in 28 alcohol-dependent patients in an outpatient setting. Although those in the supportive therapy reported lower daily drinking, there were no differences among groups on alcohol craving or randomly collected blood-alcohol levels across the three conditions.

Little research has compared group therapy to family therapy; however, a comparison of a process group therapy, family therapy, and family education for adolescents with SUDs suggested that family therapy was most effective in achieving drug abstinence (Joanning et al. 1992).

Results comparing types of group therapy have been largely inconclusive. Moreover, given dramatic variability across studies, it is difficult to make any generalizations based on the existing literature. Although some studies have found evidence for superiority of one type of group therapy over others, these results have often been limited to only certain outcomes or patient subgroups. At this time, more well-controlled studies are needed to determine what types of group therapy are most effective.

53.2.4 Comparing Group Therapies for Co-occurring Disorders

Other psychiatric disorders commonly co-occur with SUDs (Conway et al. 2006; Grant et al. 2004). Accordingly, numerous studies of group therapy for SUDs have examined therapies targeted to both the SUD and the co-occurring psychiatric disorder.

Weiss et al. (2000) compared usual care to usual care plus 12–20 sessions of an integrated group therapy for SUDs and bipolar disorder in a sample of 45 participants. Results indicated that the group therapy was associated with significantly lower SUD severity, more months abstinent, and longer durations of abstinence relative to usual care alone. In a subsequent study, 62 outpatients with co-occurring bipolar disorder and substance dependence were randomly assigned to 20 sessions of either the integrated treatment or group drug counseling (Weiss et al. 2007). Patients in the integrated group therapy had fewer days of substance use following treatment and throughout 3 months of follow-up; however, mood outcomes were similar between groups. Weiss and colleagues (2009) then tested the implementation of a 12-session version of the treatment with drug counselors without previous training in cognitive-behavioral therapy. Sixty-one participants were randomized to the integrated treatment or group counseling and results indicated better outcomes for both substance (e.g., likelihood of abstinence) and mood symptoms (e.g., greater reduction in risk for a mood episode) in the integrated treatment group.

In a study comparing dialectical behavioral therapy (DBT), which included a group therapy component, to treatment as usual for 28 women with co-occurring borderline personality disorder and substance dependence, there was significantly greater treatment adherence, more days abstinent, and more negative urine screens in the DBT group (Linehan et al. 1999). These findings for benefits of DBT were replicated in heroin-dependent women when compared to individual therapy (Linehan et al. 2002).

In a study conducted in Australia, James et al. (2004) randomized 63 participants with co-occurring alcohol or drug use and a psychotic disorder to receive either usual care and one session of substance use education or six sessions of an integrated treatment for both disorders. The integrated dual disorder treatment group was associated with significantly greater improvement in psychiatric symptoms, substance use, and SUD severity. In a similar study, Bellack et al. (2006) randomized 129 outpatients with a diagnosis of drug dependence and serious mental illness (psychotic or major affective disorder) to receive an integrated behavioral treatment (Behavioral Treatment for Substance Abuse in Severe and Persistent Mental Illness) or supportive group discussion twice weekly for 6 months. Results indicated that the integrated treatment was associated with more negative urine screens as well as better treatment retention and functional outcomes (e.g., quality of life).

Results for co-occurring depression and anxiety disorders have been more mixed. Lydecker and colleagues (2010) compared an integrated cognitive-behavioral therapy for co-occurring depression and SUDs to 12-step facilitation in a sample of 206 veterans with a current substance dependence diagnosis and

a lifetime diagnosis of major depressive disorder. Both treatments were associated with significant improvements in both depression and substance use outcomes; however, there was evidence for better maintenance of gains in reduction in substance use in the integrated treatment group.

Studies comparing Seeking Safety (Najavits 2002), an integrated treatment for co-occurring SUDs and posttraumatic stress disorder to usual care or alternative group treatments, have found both positive results (e.g., Najavits et al. 2006) and mixed results (e.g., Zlotnick et al. 2009). In a large trial of Seeking Safety, Hien et al. (2009) randomized 353 women with posttraumatic stress disorder symptoms and a diagnosis of a drug or alcohol use disorder to receive either 12 sessions of Seeking Safety or a comparison health education treatment. Results indicated significant improvement in posttraumatic stress disorder symptoms in both groups with no differences between groups and no significant effects of either treatment on alcohol or drug use outcomes; however, this may have been attributable to a low level of substance use at study entry.

Group therapy targeting co-occurring SUDs and other disorders has been successful in some cases (e.g., bipolar disorder and psychotic disorders), with more mixed results for anxiety and depressive disorders. Nonetheless, integrated group therapies are promising for the reduction of symptoms of both SUDs and co-occurring disorders and are an important area for further study.

53.2.5 How Can We Maximize Outcomes in Group Therapy?

Because the evidence generally supports the effectiveness of group therapy for SUDs, recent research has begun to examine ways to maximize its effectiveness. Several studies have tested ways to enhance group therapy by adding adjunctive interventions or manipulating group factors.

53.2.5.1 Adjunctive Treatments

Contingency management involves providing patients with reinforcers (incentives such as money or vouchers) for engaging in beneficial behaviors, such as providing negative urine drug screens or attending treatment sessions. Several studies have examined the addition of contingency management to group therapy to enhance attendance. Petry et al. (2011) examined the addition of a contingency management group to standard outpatient care (including group counseling and monitoring with urine toxicology screens) in community-based outpatient substance abuse treatment clinics. The addition of contingency management was associated with better program attendance (including more days of attendance and longer duration in treatment) and longer durations of drug abstinence. Other research has similarly found benefits of adding incentives for attending group sessions (Ledgerwood et al. 2008), although one study found only modest effects for attendance incentives (Alessi et al. 2007).

Santa Ana et al. (2007) randomized 101 dually diagnosed inpatients from a detoxification unit of a psychiatric hospital to receive two sessions of either a motivational enhancement group therapy or a group therapy control condition

in addition to standard care, to enhance adherence to aftercare. Results indicated that group motivational enhancement resulted in more aftercare sessions attended and fewer drinking days and heavy drinking days.

Studies examining the addition of adjunctive individual therapy to group therapy suggest that the benefits of this approach are modest, at best. In a large study of behavioral therapies for cocaine dependence, 487 individuals were randomized to one of four treatments, including 24 sessions of group counseling alone, or in combination with 36 sessions of one of three individual therapies: cognitive therapy, supportive-expressive psychodynamic therapy, and 12-step oriented drug counseling (Crits-Christoph et al. 1999). The best substance use outcomes were seen for the group drug counseling plus individual drug counseling intervention, followed by group drug counseling alone (Crits-Christoph et al. 2001). However, there were no differences among conditions on other functional outcomes (e.g., interpersonal functioning). Thus, the addition of individual drug counseling, and not other individual therapies, was associated with enhancement of some group therapy outcomes. Another study examined group counseling compared to group counseling plus individual relapse prevention therapy for cocaine dependence (McKay et al. 1997). Results at 6-month follow-up indicated greater likelihood of cocaine abstinence in group therapy alone, but fewer days of cocaine use among those who were not abstinent in the group plus individual therapy condition.

53.2.5.2 Intensity and Group Composition

Coviello et al. (2001) randomized 94 patients with cocaine use disorders to group therapy programs of varying intensities over a 4-week treatment program, including either 6 h of treatment (four of which were group) or 12 h of treatment (seven of which were group) per week (Coviello et al. 2001). There were no significant differences between study cohorts in terms of severity of substance use problems or other functional outcomes; on average, patients in both conditions improved on these measures.

Several studies have examined gender-specific group therapy for SUDs (e.g., Carroll et al. 1995; Copeland et al. 1993; Greenfield et al. 2007). Greenfield et al. (2007) compared a women-only relapse prevention group therapy, the Women's Recovery Group, to mixed-gender Group Drug Counseling. Results demonstrated higher satisfaction among women in the Women's Recovery Group (WRG) and similar drug use outcomes between groups. The WRG also appeared to have better alcohol use outcomes and better maintenance of gains 6 months following treatment. Moreover, the WRG seemed to have particularly beneficial effects on substance use outcomes for women with high psychiatric severity (Greenfield et al. 2008).

Several considerations may be valuable in attempting to enhance group therapy outcomes. First, adding incentives for attendance appears to enhance retention and achieve a higher dose of therapy. Second, treatment targeted to a population of interest (e.g., women) may yield added benefits relative to more general group therapy. However, studies of the addition of individual to group therapy remain somewhat inconclusive and require more study. Results to date suggest that the type of individual therapy added to group therapy may be important to determining

outcomes and that those who are not able to achieve abstinence in group therapy alone may benefit from individual therapy. Nonetheless, additional research is needed to better understand the potential benefits of combining group and individual therapies.

53.2.6 Summary and Integration of the Literature

Although research on group therapy for SUDs varies widely in the types of group therapy, substance of abuse, population of interest, and timing and delivery of treatment, several trends emerge from the existing literature. In general, studies adding group treatment to minimal or no treatment suggest that group therapy is associated with improved substance use and often also functional outcomes (e.g., Stephens et al. 2000; Weiss et al. 2000). Although not all studies have found evidence for this effect (e.g., Razavi et al. 1999), studies predominantly support group therapy as an effective intervention for SUDs. Results are mixed for adding group therapy to more powerful treatments (e.g., certain pharmacotherapies), with some evidence for no benefit for adding group therapy (e.g., Tucker et al. 2004) and others finding benefits for some outcomes or in certain subgroups (e.g., Luthar and Suchman 2000; Schmitz et al. 2007). However, many of these studies have been limited by either small sample sizes or uncontrolled designs (e.g., no limitations on additional adjunctive treatments); it thus remains unclear whether group therapy can achieve additive benefits when combined with pharmacotherapy.

Likewise, comparisons of different types of group therapy have generally yielded variable results. The relative effectiveness of different types of group treatment may depend on the fit of the intervention to the target population. For example, several integrated group therapies (such as those for SUD patients with co-occurring psychosis or bipolar disorder) have been associated with better outcomes than general alcohol and drug counseling therapies (e.g., Bellack et al. 2006; Weiss et al. 2007). Thus, the degree to which the treatment "fits" the population may be critical to understanding which treatment works best for what population.

Studies comparing individual to group delivery of substance abuse treatment (predominantly motivational enhancement or cognitive-behavioral therapy) have not found significant differences between individual and group therapy on substance use or other functional outcomes or differences in treatment retention. Although there is limited evidence for greater social functioning following group therapy (Graham et al. 1996) and greater patient preference for individual therapy (Sobell et al. 2009), the evidence overall seems to support the equivalence of these approaches for both drug and alcohol use disorders.

Given the mixed findings on effectiveness, strategies to maximize outcomes are of particular importance. The addition of incentives for attending treatment appears to improve retention, maximizing the "dose" of therapy that patients receive. Because the findings examining the addition of individual therapy to group therapy have been mixed, contingency management may be the best available strategy to enhance outcomes of group therapy.

The mixed outcomes reported above are likely due in part to the heterogeneity of studies and populations, including the dose (i.e., number of sessions) administered and the timing of when treatment occurs. In addition, many studies have used small sample sizes, which substantially limit the ability to identify differences in outcomes, particularly when comparing two active treatments, such as pharmacotherapy versus pharmacotherapy plus group therapy, or two types of group therapy. Thus, it is clear that more research is needed to understand what types of group therapy are most effective and under what conditions.

53.2.6.1 Why Is There so Little Research on Group Therapy for SUDs?

The domains of variability in conducting research on group therapy are substantial. Features such as open versus closed enrollment, group content/approach, and group composition (size and member characteristics) are all specific to group therapy research and are not relevant to studies of individual therapies. Additive designs may be of less concern than comparative designs for which conclusions about differential effects become more complicated. For example, comparing a single-gender group to a mixed-gender group might involve both differences in content (e.g., gender-specific group material) as well as composition (e.g., all women vs. men and women). Comparing individual to group therapy is even more challenging given the lack of clear guidance on equating the dosing of treatments. For example, if both group and individual sessions were 60 min, patients in individual therapy may gain a higher dose of therapy through more attention. However, if group sessions were longer, patients in group would be receiving more time in treatment. How to equivalently dose these types of therapy remains an open question (e.g., is a 90-min individual session equivalent to a 90-min group session).

The study of group therapy is also complicated by the number of potential variables that might contribute to the treatment's effectiveness. For example, active ingredients may include both the content of the group (e.g., the intervention components) and the format (e.g., group composition). Thus, studies can test one or both of these components, such as testing a group versus individual treatment or testing two types of group content or composition (e.g., single- vs. mixed-gender groups). Given the variability of studies conducted to date and – not surprisingly – variability in results, future well-designed research on group therapies will be important as we attempt to enhance outcomes and understand the best treatment approaches for patients with SUDs.

53.3 Conclusion

Group therapy is the predominant method of delivery of psychosocial treatments for SUDs. This approach is associated with lower cost than many other options as well as high satisfaction among patients. Evidence for the effectiveness of group therapy is mixed and interpretation of the literature is limited by the heterogeneity of studies and the absence of many large, well-controlled studies. Nonetheless, as a whole, group therapy appears to be an effective treatment for a range of SUDs,

particularly when the treatment is specific and well-defined; group treatment may be a particularly effective option for those with co-occurring psychiatric and substance use disorders. Studies suggest that group therapy is generally as effective as individual therapy, although the specific types of group therapy associated with the optimal outcomes remain somewhat unclear.

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From Research to Practice: The International Implementation of Multidimensional Family Therapy

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Abstract

To address a growing public health problem with youth cannabis use, five Western European countries – Belgium, France, Germany, the Netherlands and Switzerland – collaborated on a cannabis treatment research effort. After deliberation, the research priority chosen was to implement and rigorously evaluate a treatment program for adolescents with cannabis use disorders – virtually unavailable in Western Europe at the time. Adolescent cannabis use disorders were even denied by some policy makers as bona fide public health problems. The most promising candidate for the treatment program to be studied, based on cross-national expert analyses and an exhaustive review of research findings to date, was Multidimensional Family Therapy (MDFT), developed in the USA. When pilot training with candidate clinicians began, some claimed it was "too American." Some did not understand its innovation at first glance, stating that aspects of MDFT interventions were already part of daily clinical work. Others worried whether the senior role of psychiatrists would be jeopardized, and if the approach engaged in too much outreach, and would be a threat to in-office work. Still others said the model might be too practical, and ignore the need for depth-oriented, psychodynamic treatment – still dominant in parts of Europe. While at the outset MDFT presented as a cultural shock, concerns disappeared when the approach was taught, attempted and integrated into the regular practice settings. The multi-country randomized controlled trial was designed with considerable discussion and collaboration. Referred to as INCANT (International Cannabis Need of Treatment), this study, the first independent replication of MDFT, showed that most adolescents with cannabis use disorders in these five countries have multiple behavioral problems, including criminality, truancy and mental co-morbidity. MDFT proved to be more effective than a high level treatment as usual in reducing cannabis dependence and on other problem behavior measures as well. Positive outcomes were seen in all the five countries. And given the clinical outcomes, the therapist competence and fidelity outcomes, and the capacity of the sites to absorb this new clinical approach, MDFT was found to be feasible and adaptable to representative regular clinical care Western Europe settings, adding expanded treatment alternative to standard care. The challenges

of conducting a multi-national randomized controlled trial in real world, non-research settings foreshadowed subsequent efforts to sustain implementation of this evidence-based treatment program. While retaining the core principles, structure and interventions of the approach, the MDFT implementation strategy has been adapted in each of these European countries, as they vary in accreditation requirements, reimbursement rules, public and private position of treatment centers for youth with multiple problem behavior, regard for certain professional groups (e.g., social workers), and referral processes. Facilitating MDFT implementation in Europe has been like executing an EU financial crisis policy, but we are getting there.

54.1 Introduction

Adolescent health, substance misuse and correlated problem behaviors have become indisputable priorities on the global public health landscape (The Lancet 2012). But due to many intersecting issues at multiple influence levels, over two decades of scientific advances in adolescent intervention specialties have failed to yield widespread dissemination of evidence-based approaches. Standard clinical practice for drug involved youth around the world remains disconcertingly dissimilar from the evidence-based interventions reported in research journals, practitioner reviews, policy recommendations, and science-based intervention registries. Effectiveness studies and implementation trials in the adolescent treatment specialty are more frequent in recent years (Becker and Curry 2008). And, cross-national surveys and basic science research on youth substance misuse have added significantly to a useable knowledge base. But relative to need, the research-rooted knowledge about effective interventions remains underdeveloped, and at least in the treatment realm, collaborative transnational controlled trials are rare. The multisite study of Multidimensional Family Therapy (Multidimensional Family Therapy 2014a; Liddle 2010) is the first independent replication of MDFT as well as, to the best of our knowledge, the only study of its kind to date (Rigter et al. 2010, 2013; Schaub et al. 2014) – a multi-national controlled trial of an evidence-based therapy for youth substance misuse. Although an instrumental part of the contemporary process to be sure, controlled studies cannot guarantee transfer or dissemination of a program past a research project's endpoint. This article describes the implementation history, plan and outcomes of MDFT in Western Europe (Rowe et al. 2013), a research-based treatment with significant dissemination activity in the United States (Multidimensional Family Therapy 2014a) evolving into an internationally established treatment program (European Monitoring Centre for Drugs and Drug Addiction 2014b).

Before addressing implementation, we first outline key features of the clinical approach. MDFT is a comprehensive, family-centered and developmentally-oriented intervention for clinically-referred adolescents (Liddle 2010). The intervention has strong outcomes for adolescent substance abuse and delinquency in

a series of randomized controlled trials. Comparison conditions in these studies included active treatments or usual care in non-research community clinics (Hogue et al. 2014; Von Sydow et al. 2013; Williams and Chang 2000). MDFT treatment process and implementation studies (Hogue and Liddle 2009) support the model's putative mechanisms of change (Henderson et al. 2009, 2010; Hogue et al. 2008; Diamond et al. 2006; Schmidt et al. 1996), and economic analyses indicate MDFT is less expensive than standard care (Zavala et al. 2005).

The MDFT research program began with National Institute on Drug Abuse funded studies in 1985 (Multidimensional Family Therapy 2014c; Sherman 2010; Liddle 1999), and continues today at the Center for Treatment Research on Adolescent Substance Abuse (Center for Treatment Research on Adolescent Drug Abuse 2014), University of Miami, Miller School of Medicine. Core to MDFT is the idea that an adolescent's problems are influenced by interacting factors from interconnected life domains (Fogel and Thelen 1987; Gottlieb 1991; Granic and Hollenstein 2003; Thelen and Smith 1994); hence, the term "multidimensional" (Liddle and Rigter 2013). MDFT addresses four domains/systems in the life of the youth: the adolescent him- or herself, the parent(s), the family, and systems outside of the family such as friends, school, work, prosocial activities, and (when applicable) juvenile justice authorities. Improvement of functioning in all life domains helps the adolescent to abandon problem behaviors including drug taking and heavy drinking.

The approach includes interventions such as:

- Enhancing treatment engagement and motivation of the youth and parent(s)/guardian(s)
- Self examination and generation of alternatives for youth problem behavior (through individual sessions and by utilizing family support and structure)
- Relapse prevention (relative to substance abuse and other problem behaviors)
- Improving communications and relationships between family members
- Strengthening parental functioning, and parenting skills
- Coordination with other systems (school, work, justice) to facilitate positive outcomes for the youth.

MDFT is manualized but flexible. The approach has been tested and exists in different versions that vary according to individual case characteristics, treatment setting, and treatment parameters that might be dictated by the clinical setting. Guiding principles orient the clinician to treatment guidelines and protocols that specify how to conduct core sessions with the four main units of intervention – the youth, parent(s), family, and the systems of influence that are relevant to the youth's and family's current circumstances. Clinical skill and judgment remain critical within these structures. On average, there are 2 sessions per week for 4–6 months, with the adolescent alone, the parent alone, the family (parent plus youth and other family members as needed), and key parties in influential systems (e.g., school or juvenile justice) present. MDFT therapists work in teams of three to six members, including the supervisor and often a therapist assistant, who may assist with a range of community interventions.

54.2 MDFT in Europe: The History

Fifteen years ago, EU member states were debating cannabis policy. Cabinet members from five Western European countries (Netherlands, France, Belgium, Switzerland and Germany) agreed that the discourse was uninformed due to insufficient data on the effects of cannabis. A common cannabis research and development project was commissioned to fill the gaps in knowledge. Rigter was appointed project leader. A Steering Group was convened between 2000 and 2010 with representatives from the federal Ministries of Health in Belgium, Germany, the Netherlands, Switzerland, and from the government substance abuse office in France. Its work began by consulting experts from Australia, Europe, and the USA to identify cannabis research priorities, which were jointly discussed in a conference in Brussels (Spruit 2002). Based on expert recommendations, a literature review, and the Steering Committee's own deliberations, the evaluation and implementation of a treatment program for adolescents with cannabis use disorder was defined as the multi-national group's principal priority.

This decision was not undisputed. Initially, some reported that in their countries, adolescent cannabis use disorder was rarely seen, yet these countries lacked treatment services specifically for youth or mechanisms to identify adolescents with these problems. The Steering Committee opted for the aforementioned priority, understanding that most adolescents with a cannabis use disorder also manifest other problem behavior such as criminality and school failure, necessitating a treatment program to focus not only on cannabis use, but on commonly related problems as well (Spruit 2002).

Which treatment program was to be chosen? A systematic literature review was conducted (Rigter et al. 2004), from which MDFT emerged as the superior treatment candidate on the basis of its research evidence and clinical scope (Brannigan et al. 2004; Vaughn and Howard 2004). Cannabis was targeted effectively in MDFT studies in the US, and other elements of adolescent problem behavior were changed as well (Rowe 2010). The Steering Committee opted for MDFT, and MDFT developer Liddle agreed to collaborate. The Steering Group organized a meeting in Zurich in 2004, where Liddle presented MDFT to a critical jury of high ranking European addiction scientists. MDFT passed the test; the Steering Group decided to test the effectiveness of MDFT in Western Europe, and if study results warranted, follow the trial with implementation in practice. This research effort was named INCANT – International Cannabis Need of Treatment study. Steering Group members nominated outpatient clinical sites in their countries for participation in the study. To assess site interest, and viability in terms of case flow and appropriateness, clinicians' background, research capacity, and infrastructure stability, Rigter, the study Principal Investigator, Liddle and MDFT researcher and trainer Rowe made screening visits to each prospective clinical center in early Summer 2004. The selected sites for the multisite research included: Brugmann Hospital (an outpatient substance abuse treatment department of a university hospital in Brussels, Belgium), Centre Emergence (substance abuse treatment in Paris, France), Therapieladen

(substance abuse treatment in Berlin, Germany), the partnering Dutch centers of De Jutters (forensic youth [mental health] care) and Parnassia-Brijder (substance abuse treatment) in The Hague, and centers in Basel and Bern in Switzerland. All sites had links with university-based or other research institutes.

Government departments in the five countries funded a pilot study in 2005. It addressed three questions: (a) Could clinicians from the selected clinical sites be trained as MDFT therapists and supervisors, (b) Did the selected sites have sufficient access to adolescents with cannabis use disorder for INCANT recruitment purposes? and (c) Could these clinical settings conduct a rigorous community-based randomized controlled trial? These challenges were all met successfully by the clinical sites (Rigter 2005). All European candidate MDFT therapists had experience treating youth and many had strong foundations in family-based interventions. Their backgrounds varied from social workers with additional therapist training (Berlin, The Hague) to psychologists (all sites), a child and adolescent psychiatrist (Paris), and a psychiatric nurse (Brussels). In preparing for the pilot, sites debated the appropriate educational degrees of the MDFT therapist candidates (such as social work, as one example), but in the end, no specialties were excluded. Using the same standardized training methods, materials, and certification procedures developed in U.S. based controlled trials (Hogue et al. 2008), senior MDFT trainers from the Center for Treatment Research on Adolescent Drug Abuse at the University of Miami trained the diverse cohort of European clinicians in MDFT. Candidates were trained to adequate levels of adherence to MDFT protocols during the pilot study (Rigter 2005). The initial two Swiss sites had difficulties identifying appropriate referral sources for the trial and were replaced for INCANT by Phénix, an outpatient substance abuse treatment center in Geneva.

The Steering Group was satisfied with the findings of the pilot study, advising their respective government departments to fund the larger scale INCANT randomized controlled trial. The INCANT trial, initiated in 2006 and completed in 2010, compared MDFT to active individualized treatment as was routinely delivered in each site (Rigter et al. 2010). The control treatment, Individual Psychotherapy (IP), shared common elements across the five sites: therapy sessions were held only with the adolescent and targeted substance abuse and other problem behaviors. Despite commonalities, details of the IP's theoretical orientation differed among the five sites/countries. In The Hague and Brussels, IP was cognitive behavioral therapy. Psychodynamic ideas were influential with the IP clinicians in Geneva and Paris. And, IP therapists in Berlin followed a more eclectic treatment approach, borrowing from both mentioned treatment orientations.

All sites had sufficient access to adolescents with cannabis use disorder – per their usual case referrals, and sometimes via outreach and collaboration with other treatment centers (Berlin), juvenile judges (Switzerland) or media calls (Brussels). The sites would need to recruit 60–120 adolescents/families each for the INCANT trial. In the pilot and the subsequent randomized trial, sites differed in primary referral routes (Phan et al. 2011). Belgium and France recruited mainly through schools and families. In The Hague and Switzerland, most study adolescents were mandated to treatment by probation officers or other justice-related authorities.

In Berlin, the authorities offered troubled youth a sheltered living arrangement with pocket money, and some coercion to accept treatment as well (Rigter 2005).

Results of the randomized trial (n = 450) showed that across sites, irrespective of IP theoretical orientation, MDFT outperformed IP on major outcome measures. Most prominent was the larger reduction of the rate of cannabis disorder for MDFT participants compared with IP youth up to the 1 year follow-up (Rigter et al. 2013; Schaub et al. 2014). Retention rates for MDFT participants were twice as high than for IP adolescents (Rowe et al. 2013). This effect was consistent across all sites, and these clinical outcomes and retention rates are consistent with the U.S.-based trials. INCANT MDFT therapists demonstrated adherence and competence on treatment fidelity measures, suggesting that MDFT could be adopted with strong adherence in diverse cultures and systems in Western Europe (Rowe et al. 2013).

54.3 Facilitating MDFT Acceptance in European Youth Care Practice

In INCANT, MDFT proved to be transferable to the Western European locales that were part of the trial. This finding, of course, does not confirm that MDFT can be implemented and sustained in any practice setting. Making implementation work requires manpower, funding capital, persistence and tenacity, and continuous support for treatment agencies adopting the treatment program.

Next we discuss several implementation challenges, drawing from our experience with MDFT in the Netherlands, where implementation has advanced most rapidly and broadly, but also painting a broader European picture.

54.3.1 Facilitating Interest Among Therapists

For many therapists, MDFT means stretching beyond one's comfort zone: from conducting one session once every 2 or 3 weeks to doing several sessions per week; from scheduling sessions at the office to also seeing the family at their home and in the community; from a focus on one disorder or problem behavior to a comprehensive approach; from solely treatment sessions to treatment plus case management extending to all major domains in the life of an adolescent.

Difficulties in changing practice patterns are always a worry in evidence based therapy transfer. In the case of the Netherlands, for instance, we met with genuine interest from therapists all over the country. Some clinicians had their interest piqued by word-of-mouth, or by video-intensive presentations by INCANT MDFT therapists. Dissatisfaction with the outcomes and limited scope of their own professional work might have been another reason therapists were curious about and open to MDFT. The appeal of working in teams – as defined in MDFT – was another influential factor. Clinicians also learned that they could have a role in expanding MDFT services, which helped in committing them to the treatment program. Our subsequent experience with Finland has been similar in these ways.

In discussing the challenges and worries about the transfer potential of North American based prevention intervention programs in Europe, Burkhart (2013) sheds considerable light on a still to be fully illuminated process. We have also concluded that these idiosyncratic responses to an intervention's philosophy, clinical features, even training requirements and methods are among the probably many germane intervention characteristics. In France and Switzerland, for instance, we found psychodynamic traditions to remain influential and that adoption of more practical, family systems, and outcome-oriented treatment programs such as MDFT can be a stretch. Initially, concerns were voiced that one's freedom as a therapist could be curtailed by following a treatment manual. Clinical presentations by INCANT MDFT staff emphasized the how-to aspects of the approach. Aspects of clinicians' current thinking, practice habits, and previous training were used as ways to learn about a new approach. But vital to the clinician change process was a supportive and guiding type of supervision to help therapists with cases in their own clinical settings. Hardly a simple administrative decision, implementation involves multiple and intersecting processes within an organization or system of care. At the therapist level, changing a clinical mind set may involve direct or indirect challenges to ingrained views, and transforming treatment paradigms by offering training in and considerable support to learn new methods.

Perhaps there was a time when researchers believed that publication of study outcomes will yield recommendation adoption. But experience and the burgeoning literature in specialties such as implementation science demonstrate the complexity of practice change. Scientific journals do not target clinicians. Therapists need to be informed in terms relevant for daily practice. We have written MDFT materials in Dutch, English, German and French. We also produced a DVD with basic facts about MDFT and with interviews with an adolescent and his mother, therapists, and a juvenile judge (in Dutch, with English and German subtitling; see video at Multidimensional Family Therapy 2014d). Country-specific websites offer information for therapists and centers (and for teenagers and parents); see for instance (Multidimensional Family Therapy 2014e). Following a community of practice model, we update MDFT information through e-mails, e-newsletters, social media, and face to face substantive clinical meetings for therapists. But as has been the case in MDFT's dissemination in North America, materials play only a supporting role in influencing clinicians. Therapists and managers of treatment agencies experience the worth of MDFT during on-site visits. Videos demonstrate the approach in action, and live sessions with local clinicians being coached in the main MDFT methods seem critical to address their particular realities and questions. As in MDFT itself, relationships and gaining hands-on experience with the approach are instrumental.

54.3.2 The Treatment Agency

Multiple factors and levels of process interact with therapist variables to create a context of receptivity and change in adopting an evidence-based program.

The treatment agency, particularly the *manager* of the department where the MDFT team will be housed, are key in this regard. Although often interested in MDFT, managers are challenged to integrate this program, or any program for that matter, into local routines and financial structures. We facilitate this integration, a *systems intervention* in and of itself, in various ways. Implementation staff visit the management of a treatment center a few times before the contract for training is signed, and afterwards once every 6 months. In the Netherlands, we also convene regular meetings with all managers together. Topics of discussion include: (a) reimbursement of MDFT; (b) where and how to enroll cases to be treated with MDFT (referral policies, relationships with other treatment sectors); (c) how to arrange coverage for MDFT therapists to be available after regular working hours without violating labor regulations; (d) ethical and legal issues, including the protection of the privacy of clients; and (e) treatment innovation. This is all critical for implementation success. We are extending this systematic approach of administrative collaboration to other European countries.

In all Western European countries where MDFT is being implemented, treatment agencies are facing a mix of public and private policies. In the Netherlands, an agency has some leeway to choose its own course in offering treatments. In Belgium, MDFT was to be paid through federal or regional government budgets as long as the treatment was deemed 'experimental' – and anything not performed by a medical doctor will remain experimental for a long time. In Flanders at least, treatment agencies now have more freedom to opt for MDFT if insurance companies agree to pay the bill. In Germany in 2012, the federal government opened positions for treatment centers to take part in an MDFT implementation project. Major adolescent substance abuse treatment centers did apply (in Cologne, Dresden, Hamburg and Munich) and are now part of a four-center implementation effort. Without the government subsidy, these agencies would not have signed up for MDFT. Treatment innovation is difficult in Germany, because local, state and federal authorities and insurance agencies – although all supporting MDFT by now – are in deadlock about who is to take the initiative to get MDFT established and financed. An additional complication is that in Germany, therapists are expected to pay from their own pocket for any training in a new treatment program. In all other Western European countries, the treatment agency pays to train an entire MDFT team. Implementation of MDFT in Germany is proceeding, but future prospects – when the federal subsidy ends – are uncertain. Of note, too, is the position of national professional organizations, such as in Germany, the German Association for Systems Therapy and Family Therapy (DGSF). In a systematic literature review carried out under the umbrella of DGSF (Von Sydow et al. 2007), MDFT was found to be an effective therapy. DGSF is in favor of giving MDFT a place within the DGSF framework, but MDFT concepts need to be harmonized with DGSF concepts first, and this will take time. Terms like 'supervisor' have different meanings in MDFT and DGSF contexts. MDFT accreditation by DGSFT is necessary to convince therapists to personally pay for training in MDFT.

In France, the INCANT trial and ongoing liaison efforts of the MDFT team leader (Phan) combined to convince government services (MILDT; and the Ministries of Health and Justice) to support MDFT after the research study ended. Adolescent substance abuse centers were willing to meet a call to have teams of therapists trained in MDFT, with subsidy from MILDT. Teams are in training in Lille and Dijon. Teams focusing on forensic or residential care will follow in the suburbs of Paris. The aim of the French government is to have at least one MDFT team per region (country).

All in all, implementing a treatment program in a country requires adequate knowledge of national, regional and local policies and politics. Local experts must be fully on board. For lasting implementation, it does not suffice to have good research data or to win over therapists; one also needs the enduring support of the management of treatment centers and of policy makers at all levels of the youth care sector. One needs to have staff to make this happen, and to pay for that staff, one needs funding capital. In the Netherlands, we were fortunate to secure charity funding. All other European MDFT countries, except Finland, rely on government subsidies so far, which is insecure in times of economic crisis.

54.3.3 Requirements for a MDFT Program

Implementing MDFT in Europe was a joint aim of the MDFT experts at CTRADA and pioneers in Europe, headed by Rigter. MDFT developers saw throughout the INCANT pilot and trial that MDFT would disseminate throughout Europe only if the MDFT leaders in each country experienced personal ownership – a sense of being pioneers themselves. Rigter established "MDFT Academy" in 2008, a Dutch-based foundation to offer MDFT training to teams of therapists in Europe. Liddle granted MDFT Academy the free-of-charge right to train MDFT teams in Europe, provided training principles and procedures would conform to established MDFT standards developed in research trials and applied in US-based implementation efforts. MDFT representatives from Western European countries founded "MDFT Europe" in 2010, a body for agreeing on MDFT (training) practices in Europe in order to ensure consistency and uniformity.

It is made clear from the outset what it takes for a treatment institute to offer MDFT. MDFT Academy uses a set of MDFT program requirements as formulated in the MDFT manual (Liddle 2007). All MDFT supervisors and therapists must be certified (see below). Candidates for MDFT therapist training must have a university (usually psychiatrist, psychologist, pedagogue) or college (social work) degree, with additional education in psychosocial therapy. They need to have at least 3 years of experience in treating adolescents and have a basic knowledge of family therapy. An MDFT therapist is pragmatic, non-judgmental, skilful in communication, willing to work irregular hours, and receptive to feedback, seeing that there is always more to be learned. He or she is open to teamwork, intervision and supervision. The same is true of a MDFT supervisor, who also should have leadership skills.

54.3.4 Training

Important are (a) the course materials, and (b) the training interventions. The key training document is the MDFT Manual (Liddle 2007) and accompanying protocols, which have been translated in European languages (Dutch, German, French) and adapted to local practice (e.g., regulations, referral mechanisms, assessment tools as used by youth probation officers and other professionals).

American and European trainers use parallel presentation materials, core MDFT videos, and written case vignettes to cover the introductory didactic training. Instruction DVDs target the same topics, but key treatment sessions shown for training purposes are increasingly from local (Dutch, German, etc.) practice. Training interventions include plenary content and protocol review days (all trainees come together); the systematic evaluation of treatment session recordings for MDFT adherence and competence, and of supervision session recordings for supervision skills; regular site visits by the MDFT trainer to the MDFT team for on-site case review and other feedback; regular consultation telephone calls between the trainer and the supervisor and the whole team; annually, fully documenting 1 case by the trainee (session planning, case assessment, treatment plan) with feedback from the trainer; an extensive written exam; and booster training of the team and, separately, of the supervisor.

54.3.5 Certification and Licensing

The full training in MDFT takes 2 years. The Basic Level certificate is issued at the end of Year 1, the Master Level certificate after Year 2.

In Europe, teams with at least three Master Level certified members receive a free-of-charge license to practice MDFT. Once every 3 years, teams are required to refresh their license, allowing MDFT Academy to check if MDFT is still carried out properly.

54.3.6 Trainers

MDFT trainers achieve their status by developing through the ranks, first as an MDFT therapist, then supervisor, before being invited for trainership. Trainers are trained by G. Dakof (Multidimensional Family Therapy 2014b) and by MDFT Academy. At present, there are 8 Dutch trainers, 1 Flemish and 1 French-speaking trainer in Belgium, 3 trainers in Germany, 1 in France, and 1 in Switzerland.

54.3.7 MDFT Teams Trained in Europe

Between 2008 and Spring 2013, 35 Dutch teams have been trained in MDFT or are presently in training. Add to this number 2 teams in Belgium, 5 in Germany,

5 in Finland, 5 in France, and 1 in Sweden, and the European total approximates 60. There are 50 teams in the United States, yielding 110 MDFT teams worldwide.

As is the case in the U.S. uptake of MDFT, the European teams originate not only from addiction treatment, but also from youth care, mental health, and forensic settings. In Europe, MDFT has evolved beyond the narrow connotation of being an addiction treatment. In accordance with the evidence base, MDFT is seen as a treatment program for adolescents with diverse, often multiple problem behavior, regularly including delinquency and substance abuse.

54.3.8 Accreditation

'Accreditation' in Europe requires that a treatment program is evidence-based. Although MDFT is included in North American evidence-based practice registries (Substance Abuse and Mental Health Services Administration 2014; Sherman 2010; Crime Solutions 2012; Division 53, American Psychological Association 2012; California Evidence-Based Clearinghouse 2012), European policy makers and scientific bodies are keen to make their own assessments. In the Netherlands, approval by the National Accreditation Committee on Justice-Related Behavioral Interventions is required for the Ministry of Justice to fund forensic treatment settings. This Committee uses ten criteria to evaluate interventions. The treatment program must be effective and should be based on a strong theory explaining how multi-problem behavior arises. Risk and protective factors are to be specified and clearly linked to concrete interventions, including skills training. The treatment program must be phased, with emphasis on motivating cases in the beginning and on providing continuity of care at the end. The program should include quality assurance control, making sure it is carried out competently, and should adhere to the therapy's basic principles. MDFT Academy filed the dossier requested and, in 2011, the Committee mentioned accredited MDFT. The Netherlands Youth Institute (NJI) followed suit, and has accredited MDFT for use in all youth care sectors. Although other European countries have less formal mechanisms of accreditation, they may use, at least in part, the positive verdicts in the Netherlands.

Accreditation is not just an issue of individual European countries. The EMCDDA (European Monitoring Centre of Drugs and Drugs Abuse) is the European Union 'drug tsar' office, so to speak. The EMCDDA reviewed adolescent drug abuse treatment programs and affiliated researchers conducted meta-analyses. MDFT outcomes were judged to be strong (European Monitoring Centre for Drugs and Drug Addiction 2014a), and this independent evaluation is consistent with others that support the individual studies and overall research base of MDFT.

54.3.9 Reimbursement

Accreditation is the green light for funding agencies to pay for a treatment program. MDFT is now being paid from all relevant reimbursement schemes in the

Netherlands and Finland, including government sources and private health and social insurance companies. It is being funded by the (federal) governments in Belgium, Germany and France, yet a challenge here is to convince insurance companies and local authorities to take over reimbursing MDFT.

54.3.10 Innovation

A treatment program that is inflexible because it is based on just one protocol-dictated model application will not meet lasting approval of therapists in the heat of their daily work. A treatment program that is open to innovations in practice that will both retain model fidelity and address local needs is more likely to be accepted widely by practitioners.

In Europe, we regularly get feedback from trainees such as: MDFT is wonderful, but I work in setting X or Y (for instance, residential youth care, or a day treatment program) or with a special population such as adolescents with sub-normal IQ (mild mental handicap) or with emerging signs of other mental disorders. And then they ask: Can MDFT be made applicable in those settings and for those target groups as well? The answer often is not a simple yes or no. We will carefully assess the possibilities of developing new applications of MDFT, and will accept the challenge if the prospects are good and if we have the proper means (manpower, time, money, interested treatment centers).

Special 'modules' have been developed in the Netherlands for incorporating MDFT in residential settings, such as juvenile detention centers or residential youth care institutes. The aim is to start with MDFT during intramural residency of the youth, and to continue this program on an outpatient basis once the youth has been released. This approach is also pursued in the USA, for instance through the DTC (Detention to Community) project (Liddle 2010). One other novel application of MDFT is to offer the therapy to adolescents/families on an outpatient basis to avoid residential out of home placement of the youth (Henderson et al. 2011). In 2011, the MDFT team of one residential youth care institute in the Netherlands succeeded in convincing 81 % of referred adolescents/families to opt for outpatient MDFT rather than for the indicated residential placement. None of these adolescents who participated in the outpatient alternative required out of home placement post treatment.

54.4 Conclusion

Implementation is complex, hard work. We have given an overview of MDFT implementation hurdles and breakthroughs in Europe. MDFT has been disseminated in the Netherlands more quickly than in other European countries, because there was money to fund training infrastructure and start up activities. Other European countries are now gearing up, with continued MDFT dissemination to be seen in the next few years.

One might say that these other European countries could replicate the Dutch model, but this would be a misapprehension of implementation realities. The exact path traveled in the Netherlands will not necessarily work in Belgium, Finland, France, Germany, Switzerland, or any other country. Implementation should always acknowledge the basic principles of the treatment program but procedures must and can be adapted to local circumstances.

International collaboration can speed up implementation. There is close working relationship between European stakeholders in disseminating MDFT and setting quality standards, and there is tight collaboration between Europe and the source of MDFT, the USA (www.mdft.org). Important here has been the decision of the MDFT personnel to consider this treatment program as a public asset rather than a commercial product.

The implementation outcomes of MDFT in a European context discussed in this chapter and elsewhere (Rowe et al. 2013) add to published reports of MDFT implementation in the U.S. (Liddle et al. 2002, 2006). These studies showed that MDFT can be successfully transported to usual care American juvenile justice, mental health, and addiction care settings with multi-ethnic youth presenting with a range of problem behaviors (substance abuse, delinquency, symptoms of other mental and behavioral disorders), and taught to staff from various professional backgrounds (psychiatrists, psychologists, social workers, nurses, juvenile justice court staff, judges, lawyers) (Liddle et al. 2006).

The pursuit of international projects that have included independent replication of previous outcomes contributes to a treatment system's development, and offers another metric by which its usefulness can be assessed. The knowledge base about how an intervention should and can be adapted, culturally, emerging institutionally (systems of care), or procedurally (intervention structure, methods), are in an early developmental stage. Although guidance is emerging about the international transport of evidence-based interventions, numerous controversies have been specified as well (Andréasson 2010). International work, like travel in general (De Botton 2002), offers perspective and insight unavailable at home. In the case of MDFT, the international implementation described in this chapter offers a case study of the complex and sensitive intervention adoption process. This effort has enriched our knowledge of the change principles that guide clinical work with adolescents and families across cultures and settings, and our dissemination work as well.

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Couples Therapy in Treatment of Alcoholism and Drug Abuse

55

Timothy J. O'Farrell

Contents

Abstract

Couples therapy has been developed and studied as an approach to treating married or cohabiting individuals seeking help for alcoholism or drug abuse, starting in the 1970s. Behavioral Couples Therapy (BCT) is a specialized form of couples therapy that has received substantial research support. BCT sees the substance-abusing patient together with the spouse or live-in partner for outpatient couple counseling sessions. BCT aims to build support for abstinence

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and to improve relationship functioning. BCT promotes abstinence with a "recovery contract" that involves both members of the couple in a daily trust discussion ritual to reward abstinence. BCT improves the relationship with techniques for increasing positive activities and improving communication.

Research shows that BCT produces greater abstinence and better relationship functioning than typical individual-based treatment and reduces domestic violence and emotional problems of the couple's children. Most research on BCT has been done in the USA. Four BCT studies have been done internationally outside the USA, in Canada, India, the Netherlands, and Australia. Despite the promise of BCT in countries that have developed health and addiction services, it seems unlikely that countries with less developed health systems would make use of BCT as currently practiced in the USA. Possibly, some components of BCT – such as the daily trust discussion in which the addicted person states their intention not to use that day to a family member who thanks the person for their efforts – might be adapted for use more broadly.

55.1 Introduction

Historically, alcoholism and drug abuse have been viewed as individual problems best treated on an individual basis. However, over the past 35 years, there has been a growing recognition that couple and family relationship factors often play a crucial role in understanding and treating substance abuse. *Behavioral Couples Therapy* (i.e., "BCT") for alcoholism and drug abuse is one approach that has developed out of this recognition.

Viewed from a couple perspective, there are several antecedent conditions and reinforcing consequences of substance use. Poor communication and problem-solving, arguing, lying and distrust, financial stressors, and nagging are common antecedents to substance abuse. Additionally, caretaking by the non-substance-abusing spouse following drinking or drug use can inadvertently reinforce substance use. Further, spouses' resentments, while understandable, can lead to ignoring rather than reinforcing abstinence. BCT was designed to address these couple factors in the recovery process.

55.2 Behavioral Couples Therapy

55.2.1 Description of the Approach

55.2.1.1 Overview of BCT

Behavioral Couples Therapy (BCT) was designed for married or cohabiting individuals seeking help for alcoholism or drug abuse. BCT sees the substance-abusing patient together with the spouse or live-in partner. Goals of BCT are to build support for abstinence and to improve relationship functioning. BCT promotes abstinence with a recovery contract that involves both members of the couple in

Table 55.1 Components of *recovery contract*

Daily trust discussion
Alcohol/drug abuser states intention to stay abstinent *that day*
Spouse thanks alcohol/drug abuser for efforts to stay abstinent
Patient thanks spouse for support
Couple does not argue about past or future substance use
Medication to aid recovery
Self-help involvement
Weekly urine drug screens
Other weekly activities to support recovery
Progress recorded on calendar

a daily trust discussion ritual to reward abstinence. BCT improves the relationship with techniques for increasing positive activities and improving communication. BCT also fits well with 12-step or other self-help groups, individual or group substance abuse counseling, and recovery medications. BCT can be easily integrated into a variety of orientations to addiction treatment, including 12-step and cognitive-behavioral addiction programs.

BCT is founded on two fundamental assumptions. First, family members can reward abstinence. Second, relationship distress and conflict are powerful triggers for substance abuse and reduction of these triggers improves treatment outcomes. BCT typically consists of 12–20 weekly outpatient couple sessions over a 3–6-month period. Generally, couples are married or cohabiting for at least a year, without current psychosis, and one member of the couple has a current problem with alcoholism and/or drug abuse. The couple starts BCT soon after the substance abuser seeks help. BCT can start immediately after detoxification or a short-term intensive rehab program or when the substance abuser seeks outpatient counseling. The remainder of this section on clinical procedures for BCT is written in the form of instructions to a counselor who wants to use BCT.

55.2.1.2 Building Support for Abstinence with the Recovery Contract

BCT uses a recovery contract as a major support for abstinence. The first part of the contract is the "daily trust discussion" in which the patient states his or her intent not to drink or use drugs that day (in the tradition of "one day at a time"), the spouse expresses support for the patient's efforts to stay abstinent, and the patient thanks the spouse for the encouragement and support. For patients taking a recovery-related medication (e.g., disulfiram, naltrexone), this is done as part of the trust discussion. The spouse records performance of the trust discussion and other recovery supports (self-help meetings, drug screens, medication) on a calendar that is provided. The calendar provides an ongoing record of progress that the therapist reviews and praises at each session. Finally, the couple agrees not to discuss substance-related conflicts which can trigger relapse, reserving these discussions for the counseling sessions. Table 55.1 summarizes the components of the recovery contract.

Typically, it takes three or more sessions before the contract goes smoothly. In the first BCT session, the couple rehearses the trust discussion part of the contract in

session and agrees to try it each day for the coming week at home. In the next BCT session, if they did it faithfully at home, the couple signs the contract for a specific time period. In each subsequent BCT session, the counselor reviews the contract performance in the past week and the couple does the trust discussion in session to highlight its importance. Self-help meetings, drug urine screens for patients with a current drug problem, and recovery-related medication are part of the contract for many patients – each activity helps the patient stay abstinent and demonstrates to the spouse the patient's commitment to abstinence and a changed lifestyle.

It is important for couples to see that the recovery contract does not conflict with 12-step beliefs. For patients, stating that they do not intend or plan to drink or use drugs in the next 24 h does not constitute a guarantee or conflict with having a disease over which they are powerless. For spouses, being part of the trust discussion or observing the patient take recovery medication in no way makes them responsible for the patient's recovery.

Recovery Contract Case Example #1

Figure 55.1 presents the recovery contract and calendar for Mary Smith and her husband Jack. Mary was a 34-year-old teacher's aide in an elementary school who had a serious drinking problem and also smoked marijuana daily. She was admitted to a detoxification unit at a community hospital after being caught drinking at work and being suspended from her job. Her husband Jack worked in a local warehouse and was a light drinker with no drug involvement. Mary and Jack had been married for 8 years, and Jack was considering leaving the marriage, when the staff at the detoxification unit referred them to the BCT program.

The therapist developed a recovery contract in which Mary agreed to a daily "trust discussion" in which she stated to Jack her intent to stay "clean and sober" for the next 24 h and Jack thanked her for her commitment to sobriety. The couple practiced this ritual in the therapist's office until it felt comfortable and then also performed the discussion at each weekly therapy session on Wednesday evening. As the calendar in Fig. 55.1 shows, they did this part of the contract nearly every day, missing only on an occasional Saturday because their schedule was different that day and sometimes they forgot. Mary agreed to at least two AA meetings each week and actually attended three meetings per week for the first 2 months.

Jack was pleased to see Mary staying sober and going to AA. However, he was upset that weekly drug urine screens were positive for marijuana for the first few weeks, taking this as evidence that his wife was still smoking marijuana even though she denied it. The therapist explained that marijuana could stay in the system for some time particularly in someone who had been a daily pot smoker. The therapist suggested Jack to go to Al-Anon to help him deal with his distress over his wife's suspected drug use. After a few weeks, the drug screens were negative for marijuana and stayed that way lending further credence to Mary's daily statement of intent. Jack found Al-Anon helpful and the couple added to their contract that one night a week they would go together to a local church where Mary could attend an AA meeting and Jack an Al-Anon meeting.

Recovery Contract Case Example #2

If both members of a couple have a current substance problem and both want abstinence, then BCT often is workable. This was the case of Sue and Gene – a dual-problem couple. Sue came to BCT after detox for heavy daily drinking plus cocaine and marijuana 3–4 times per week. Gene had similar problems but did not need detox.

RECOVERY CONTRACT

In order to help (patient) Mary with his/her recovery and to bring peace of mind to (partner) Jack, we commit to the following:

Patient's Responsibilities	Partner's Responsibilities
☒ DAILY TRUST DISCUSSION (with medication N.A. if taking it)	
• States his/her intention to stay substance free that day (and takes medication if applicable).	• Records that the intention was shared (and medication taken if applicable) on calendar.
• Thanks partner for supporting his/her recovery.	• Thanks patient for his/her recovery efforts.
☒ FOCUS ON PRESENT AND FUTURE, NOT PAST	
• If necessary, requests that partner not mention past or possible future substance abuse outside of counseling sessions.	• Agrees not to mention past substance abuse or fears of future substance abuse outside of counseling sessions.
☒ WEEKLY SELF-HELP MEETINGS	
• Commitment to 12-Step mtgs: AA mtgs 7pm Tues at church 10am Sat at hospital	• Commitment to 12-Step mtgs: Al-Anon mtg 7pm Tues at church
☒ URINE DRUG SCREENS	
• Urine Drug Screens: weekly at counseling sessions	
☐ OTHER RECOVERY SUPPORT	
• _____	• _____

EARLY WARNING SYSTEM

If, at any time the trust discussion (with medication if taking it) does not take place for two days in a row, we will contact (therapist/phone #: Dr. Tim O'Farrell 123-456-7899) immediately.

LENGTH OF CONTRACT

This agreement covers the time from today until the end of weekly therapy sessions, when it can be renewed. It cannot be changed unless all of those signing below discuss the changes together.

Mary Smith
Patient

Jack Smith
Partner

Tim O'Farrell Ph. D.
Therapist

9 / 12 / xx
Date

Fig. 55.1 (continued)

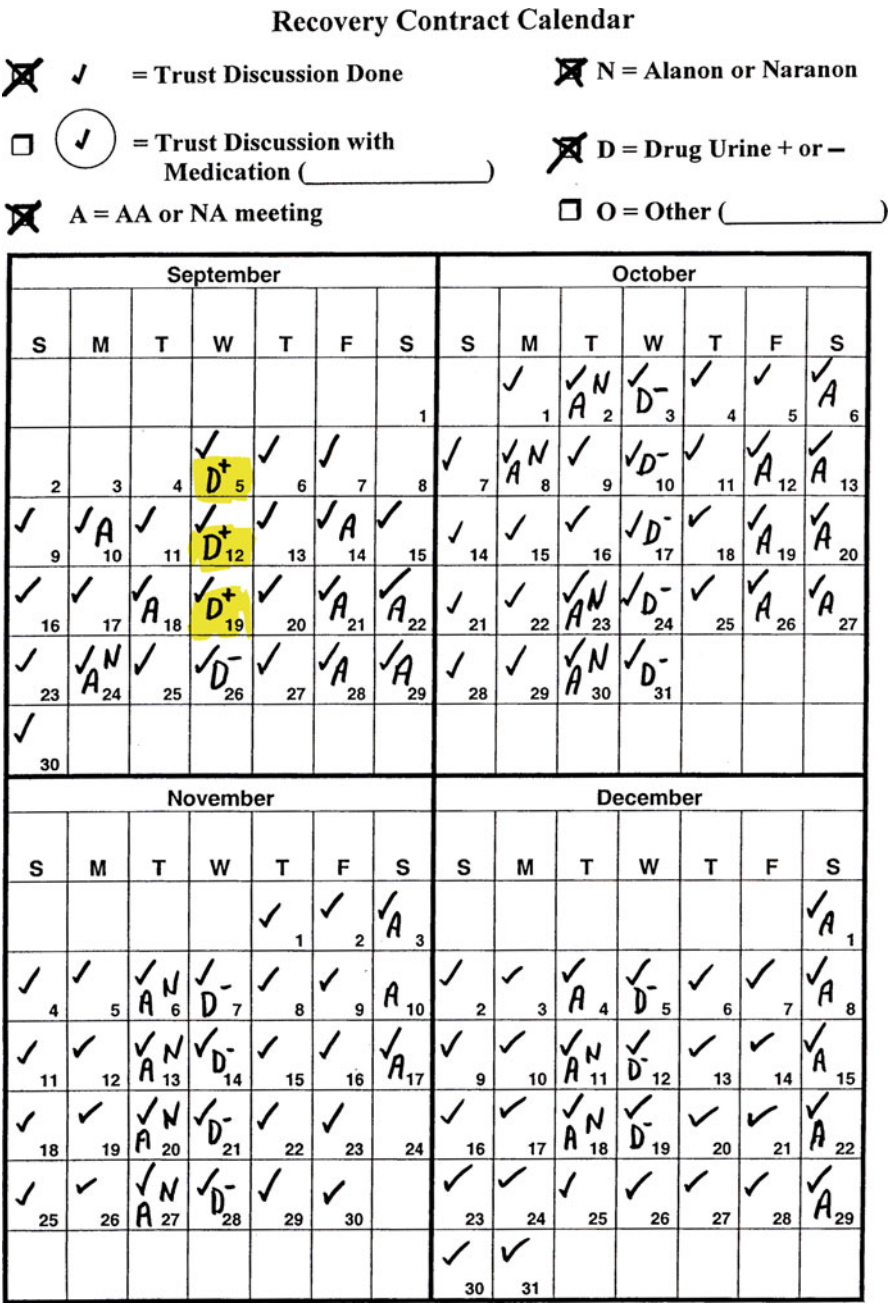

Fig. 55.1 Recovery contract and calendar for Mary and Jack (Reprinted from O'Farrell and Fals-Stewart (2006), p. 48. Used with permission)

Both wanted to "quit for good" to get their three school-age children back. Sue's parents were given temporary custody when Gene was arrested for drunk-driving. Sue, also intoxicated, and the kids were in the car. Sue and Gene had 6 months of weekly BCT. Their "dual recovery contract" shown in Fig. 55.2 had (1) a daily trust discussion, (2) taking Antabuse daily together, (3) three AA meetings per week, and (4) weekly urine screens.

About 5 weeks after starting BCT, Sue used cocaine on Friday night when she went to the local bar with a girlfriend. At the next BCT session, her urine was positive for

DUAL RECOVERY CONTRACT

In order to help with their recoveries Sue and Gene agree to the following.

Sue's Responsibilities	Gene's Responsibilities
☒ DAILY TRUST DISCUSSION (with medication if taking it)	
• States intention to stay substance free that day (takes medication Antabuse if applicable).	• States intention to stay substance free that day (takes medication Antabuse if applicable).
• Thanks partner for recovery efforts and support.	• Thanks partner for recovery efforts and support.
• Records these actions on calendar.	Records these actions on calendar.
☒ FOCUS ON PRESENT AND FUTURE, NOT PAST	
• Agrees not to mention partner's past substance abuse or fear about future use.	• Agrees not to mention partner's past substance abuse or fear about future use.
☒ WEEKLY SELF-HELP MEETINGS	
• Commitment to 12-Step mtgs: AA mtgs 3x/wk	• Commitment to 12-Step mtgs: AA mtgs 3x/wk
☒ URINE DRUG SCREENS	
• Urine Drug Screens: weekly at couple sessions	• Urine Drug Screens: weekly at couple sessions
☐ OTHER RECOVERY SUPPORT	
•	•

EARLY WARNING SYSTEM

If, at any time the trust discussion (with medication if taking it) does not take place for two days in a row, we will contact (therapist/phone #: Dr. Tim O'Farrell 123-456-7899) immediately.

LENGTH OF CONTRACT

This agreement covers the time from today until the end of weekly therapy sessions, when it can be renewed. It cannot be changed unless all of those signing below discuss the changes together.

Sue Jackson — Gene Jackson

Tim O'Farrell Ph.D. — Therapist

9 / 3 / xx — Date

Fig. 55.2 (continued)

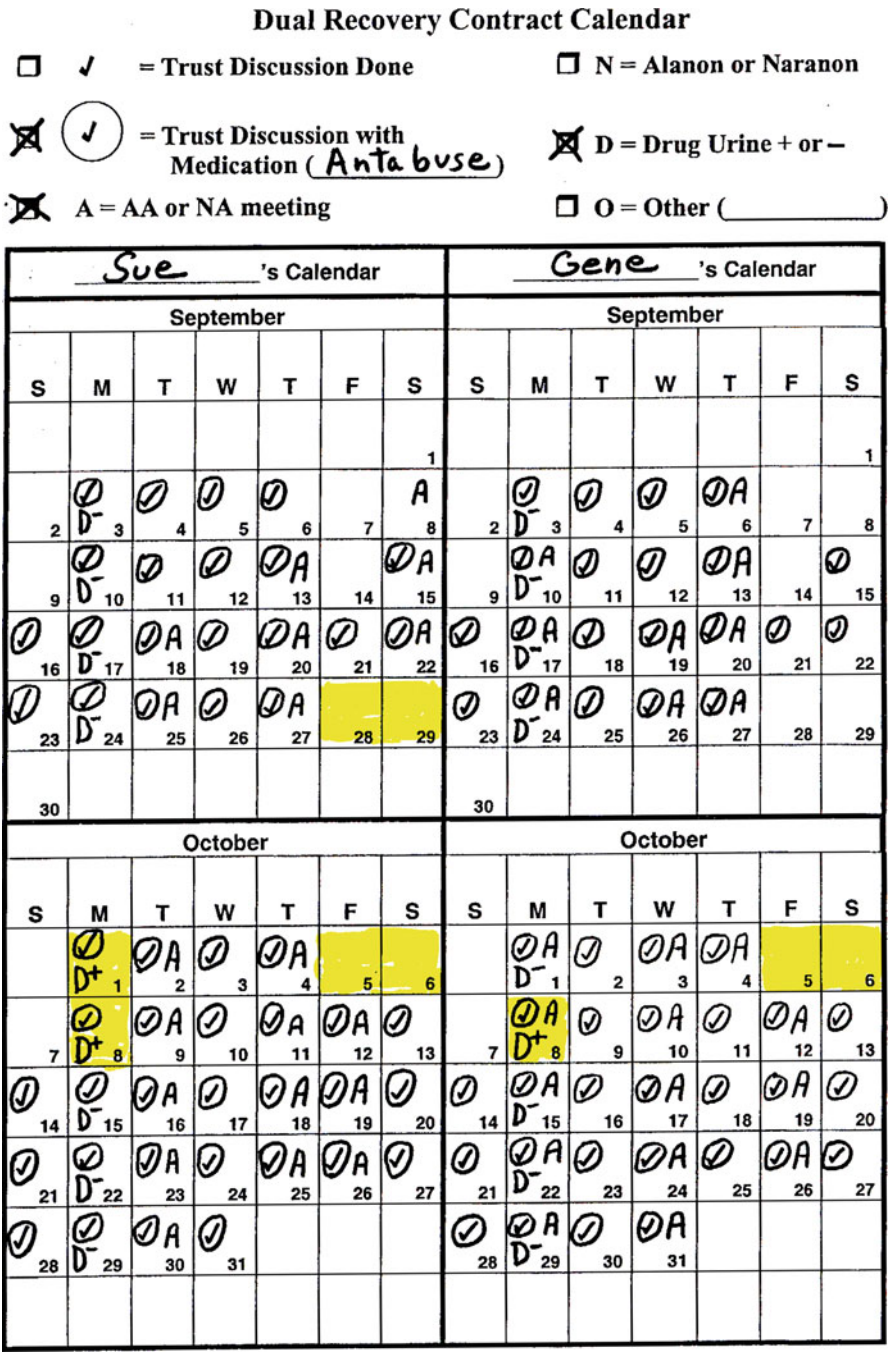

Fig. 55.2 Recovery contract and calendar for Sue and Gene, a dual-problem couple (Reprinted from O'Farrell and Fals-Stewart (2006), p. 201. Used with permission)

cocaine. The following Friday, they were both found in the bar. They planned to just socialize, but when cocaine was offered, they did not refuse, but just did one line of cocaine each. The next night, they went to the bar again and each used multiple lines of cocaine. This relapse was a turning point. They got more committed to their recovery. They planned things to do Friday and Saturday nights, starting with an AA meeting together on Friday night. Each got a sponsor and some sober friends.

After weekly BCT, they had quarterly checkups for two more years. They regained custody of their children and stayed abstinent except for a few isolated days for Gene and a 5-day relapse for Sue, which led to a few crisis sessions with the BCT counselor to help them get back on track.

Other Support for Abstinence

Reviewing urges to drink or use drugs experienced in the past week is part of each BCT session. This includes thoughts and temptations that are less intense than an urge or a craving. Discussing situations, thoughts, and feeling associated with urges helps identify potential triggers or cues for alcohol or drug use. It can help alert the therapist to the possible risk of a relapse. It also identifies successful coping strategies (e.g., distraction, calling a sponsor) the patient used to resist an urge, and it builds confidence for the future.

Crisis intervention for substance use is an important part of BCT. Drinking or drug use episodes occur during BCT as with any other treatment. BCT works best if you intervene before the substance use goes on for too long a period. In an early BCT session, negotiate an agreement that either member of the couple should call you if substance use occurs or if they fear it is imminent. Once substance use has occurred, try to get it stopped and to see the couple as soon as possible to use the relapse as a learning experience. At the couple session, you must be extremely active in defusing hostile or depressive reactions to the substance use. Stress that drinking or drug use does not constitute total failure and that inconsistent progress is the rule rather than the exception. Help the couple decide what they need to do to feel sure that the substance use is over and will not continue in the coming week (e.g., restarting recovery medication, going to AA and Al-Anon together, reinstituting key elements of the recovery contract, entering a detoxification unit). Finally, try to help the couple identify what trigger led up to the relapse and generate alternative solutions other than substance use for similar future situations.

55.2.1.3 Increasing Positive Activities to Improve the Relationship

Most substance abuse patients need help to improve their relationships. BCT works to improve the couple's relationship functioning by increasing positive couple and family activities and teaching communication skills. Table 55.2 summarizes BCT interventions for improving the couple's relationship. We will consider positive activities first.

BCT aims to increase positive couple and family activities in order to enhance positive feelings, goodwill, and commitment to the relationship. BCT methods used to increase positive activities include "catch your partner doing something nice," "shared rewarding activities," and "caring days."

Table 55.2 Improving the *relationship in BCT*

Increasing positive activities
Catch your partner doing something nice
Shared rewarding activities
Caring day assignment
Teaching communication
Listening skills
Expressing feelings directly
Communication sessions

Catch Your Partner Doing Something Nice

Couples struggling with substance abuse often complain that love and caring have gone out of their relationship. This procedure can help couples begin to change this state of affairs. Catch your partner doing something nice makes both members of the couple more aware of the benefits they are already getting from the relationship. It increases how often the man and woman notice and acknowledge pleasing or caring behaviors on a daily basis.

Specifically, Catch your partner doing something nice asks each person to notice and acknowledge one nice thing each day that their partner did. They can do the daily acknowledging when they do the trust discussion at home. Also, they should practice during BCT sessions acknowledging their partner's most pleasing behavior in the prior week.

Shared Rewarding Activities

The upset and unhappiness that comes with a substance abuse problem can cause a couple to stop doing things together. Often, a pattern develops where the couple spends less time together, becoming more distant from each other, and the patient spends more time using substances. They no longer do activities they once enjoyed. The spouse often fears that the substance-abusing member will get intoxicated and embarrass the family. They may not enjoy each other's company anymore. The goal of shared rewarding activities is to reverse this pattern and to put fun back in the relationship.

The couple starts by making a list of possible activities. Each activity must involve both spouses, either by themselves or with their children or other adults and can be at or away from home. Then, the couple plans an activity to do in the coming week. Finally, the couple is encouraged to refrain from discussing problems or conflicts during their planned activity.

Increasing shared fun activities helps both the couple's relationship and the patient's recovery. Shared fun activities can bring the couple closer together. In addition, patients who do enjoyable substance-free activities with their spouse and children have better recovery rates after substance abuse treatment (Moos et al. 1990).

Caring Day

In the caring day assignment, each person plans ahead to surprise their partner with a day when they do some special things to show their caring. This can involve doing a number of little things throughout the day or a bigger, special gesture of caring.

This is important because the stress and unhappiness of living with substance abuse often causes partners to hold back caring actions and feelings out of anger and disappointment. Therefore, active efforts like caring day are needed to increase caring and to help repair the damage done to the relationship by the substance abuse and other problems. The BCT therapist encourages each partner to take risks and to act lovingly toward the spouse rather than wait for the other to make the first move.

55.2.1.4 Teaching Communication Skills to Improve the Relationship

Inadequate communication is a major problem for alcoholism and drug abuse patients and their spouses. Once the patient is abstinent, inability to resolve conflicts and problems can cause substance abuse and relationship tensions to recur. Teaching couples how to resolve conflicts and problems can reduce family stress and decrease risk of relapse. BCT teaches communication skills of effective listening and speaking and use of planned communication sessions.

As BCT defines it, good communication exists when the intended message of the speaker matches the message received by the listener. Barriers to good communication include (1) "filters" that affect how the listener interprets the speaker's message and (2) the "All Talk and No Listen" syndrome when both partners think they are right and are unwilling to listen to each other. The BCT therapist emphasizes that the couple needs to learn both "listening" and "speaking" skills.

Listening Skills

Effective listening helps each spouse to feel understood and supported. It slows down couple interactions to prevent quick escalation of angry exchanges. The listener restates and checks the accuracy of the message received from the speaker (*What I heard you say was _____. Did I get that right?*). When the listener has understood the speaker's message, roles change and the first listener then speaks. Teaching a partner to communicate support and understanding by summarizing the spouse's message and checking the accuracy of the received message before stating their own position is often a major accomplishment that has to be achieved gradually.

Expressing Feelings Directly

Effective speaking skills consist of expressing positive and negative feelings directly using "I" messages:

I feel _____ (emotion), when you _____ (behavior), because _____ (specific reason).

After presenting the rationale and instructions, the therapist models correct and incorrect ways of expressing feelings and elicits the couple's reactions to these modeled scenes. Then, the couple role-plays a communication session in which spouses take turns being speaker and listener, with the speaker expressing feelings directly and the listener using the listening response. During this role-playing, the therapist coaches the couple as they practice reflecting the direct expressions of

feelings. Next, the therapist assigns for homework similar communication sessions, 10 to 15 min each three to four times weekly. Subsequent therapy sessions involve more practice with role-playing, both during the BCT sessions and for homework.

Communication Sessions

These are planned, structured discussions used for in-session and at-home practice of communication skills. The couple talks privately, face-to-face, without distractions. Each spouse takes turns expressing their point of view without interruptions.

The therapist discusses with the couple when and where they plan to have their assigned communication practice sessions. Assess the success of this plan at the next session, and suggest any needed changes. Just establishing a communication session as a method for discussing feelings, events, and problems can be very helpful for many couples.

Communication training in BCT starts with positive or neutral topics and then switches to real problems, first on less sensitive issues and finally working up to major charged issues. Before the couple learns how to negotiate charged issues "on their own," the BCT therapist is a very active negotiator, problem-solver, and guide to help the couple find at least temporary solutions to heated conflicts that arise.

55.2.1.5 Relapse Prevention and Continuing Recovery in BCT

Most couples who attend BCT sessions faithfully experience a period of stable abstinence and get along better while they are attending the weekly BCT sessions. BCT provides a supportive structure. It encourages couples to do many actions that support recovery for the substance abuser and for the relationship. However, when the structure of the weekly BCT sessions ends, there is a natural tendency for backsliding. Many couples stop or decrease activities that supported recovery and find themselves vulnerable to relapse. Therefore, it is critical to help couples maintain the gains they made in BCT and prevent or minimize relapse.

Once it has been determined that weekly BCT sessions will be ending soon, the therapist helps the couple prepare for this. This involves completing a Continuing Recovery Plan that specifies activities to do to maintain abstinence and relationship recovery after weekly couple sessions end. In this plan, the couple chooses which activities from previous BCT sessions they wish to continue (e.g., daily trust discussion, AA meetings, shared rewarding activities, communication sessions).

To prevent relapse, BCT helps couples to identify upcoming situations that might increase the risk for relapse and develop a plan of action for addressing them. In addition, BCT helps couples to identify early warning signs of relapse (e.g., stopping self-help attendance, changes in mood) and a plan for addressing these problems. Also, BCT therapists help couples to identify sources of support for coping with relapses (e.g., AA sponsors, friends) and how to get help from others during these events. Couples are encouraged to contact the BCT therapist if a relapse were to occur, so that the therapist can help the couple to navigate this issue and minimize the relapse.

After weekly BCT ends, couple checkup visits with the counselor every few months for an extended period can encourage continued progress. These ongoing contacts can review the couple's success with continuing activities to promote recovery and with their action plan to prevent or minimize relapse. These contacts also help to evaluate whether there is a need for additional BCT sessions.

Couples who have more severe problems or who had trouble during weekly BCT sessions may benefit from more frequent "booster session" contacts in the year after weekly BCT ends. Such BCT booster sessions seek to maintain gains achieved during weekly BCT, deal with problems that are still unresolved or that emerge later, and prevent or minimize relapse (O'Farrell 1993). Research shows that BCT with booster sessions produces better drinking outcomes than standard BCT, with the benefits of BCT booster sessions especially evident for couples with more severe addiction problems (O'Farrell et al. 1998).

Finally, continued contacts with the couple can address relationship issues still unresolved or those that emerge later. This is important because many substance abusers continue to have relationship problems even after a period of stable abstinence has been established, and couple and family issues often appear after a period of recovery.

55.2.1.6 Contraindications for BCT

A few contraindications for BCT should be considered. First, couples in which there is a court-issued restraining order for the spouses not to have contact with each other should not be seen together until the restraining order is lifted or modified to allow contact in counseling.

Second, couples are excluded from BCT if severe intimate partner violence (IPV) has occurred in the past 2 years or if one or both members of the couple fear that taking part in couples treatment may stimulate violence. Although IPV is quite common among substance abuse patients, most of this violence is not so severe that it precludes BCT. The best plan in the vast majority of cases is to address the violence in BCT sessions by teaching a commitment to nonviolence, communication skills to reduce hostile conflicts, and coping skills to minimize conflict if the substance abuser relapses (for details, see O'Farrell and Fals-Stewart 2006; O'Farrell and Murphy 2002). Research reviewed below shows that violence is substantially reduced after BCT and virtually eliminated for patients who stay abstinent.

Finally, if both members of the couple have a current substance abuse problem, BCT may not be effective. In the past, if both members of a couple had a substance abuse problem, we would not treat them together unless one member of the couple has at least 90 days abstinence. However, in a recent project, we successfully treated couples in which both the male and female partner had a current alcoholism problem and both wanted to work together in BCT to get sober (Schumm et al. 2012). Thus, if both members of the couple want to stop drinking or if this mutual decision to change can be reached in the first few sessions, then BCT may be workable. Case example #2 earlier in this chapter illustrates the successful use of BCT with such a dual-problem couple.

55.2.2 Evidence to Support the Approach

Most of the research on BCT has focused on two *primary outcomes*, namely, substance use and relationship functioning. This is understandable, given that BCT for substance abuse is designed primarily to have a direct effect on these areas of functioning. However, studies show that BCT has broader effects on important *secondary outcomes*, including reduced partner violence and improved adjustment for children of couples getting BCT. These are called secondary outcome domains, not to diminish their importance but rather to signify that these outcomes were not the primary targets of the initial BCT intervention.

55.2.2.1 BCT Primary Clinical Outcomes: Abstinence and Relationship Functioning

The primary goals of BCT are to build support for abstinence and to improve relationship functioning among married or cohabiting individuals seeking help for alcoholism or drug abuse. Primary clinical outcome domains examined in randomized studies of BCT reflect these goals. Improved substance use outcomes include measurement of days drinking or using drugs and extent of substance-related problems. Improved relationship functioning generally is measured with relationship adjustment questionnaires. A meta-analysis of 12 controlled studies found that BCT produced better substance use and relationship outcomes than more typical individual-based treatment (IBT) for married or cohabiting alcoholic and drug-abusing patients. This meta-analysis showed a medium effect size favoring BCT over individual treatment (Powers et al. 2008). An expanded and updated meta-analysis reported similar findings (Meis et al. 2013). It should be noted that a medium effect size is considered a clinically significant difference (Rosenthal 1991) when evaluating health-related interventions.

Schumm et al. (2014) is the latest BCT study. It is presented here as an example. This study conducted a randomized clinical trial comparing BCT plus IBT with IBT alone for women alcoholic patients. Married or cohabiting female alcohol-dependent patients ($N = 105$) seeking outpatient treatment in the Boston area were randomly assigned to 26 treatment sessions over a 20-week period consisting of either (a) BCT plus 12-step oriented IBT or (b) IBT for the patient alone. Outcome data were collected from patients and spouses during and immediately after treatment and at quarterly follow-ups for 12 months after treatment. Results in the year after treatment showed that BCT patients, when compared with their IBT-only counterparts, had more days abstinent, fewer substance-related problems, and greater relationship happiness by the male partner. The Schumm et al. results are significant because they add to the studies showing that BCT is effective with both women and men substance-abusing patients.

55.2.2.2 BCT and Intimate Partner Violence Outcomes

Intimate partner violence (IPV) is a major problem among men and women entering treatment for substance use disorders (Chase et al. 2003; Stuart et al. 2009). In two naturalistic studies of male alcoholics, male-to-female IPV was significantly

reduced in the first and second year after BCT and nearly eliminated with abstinence. O'Farrell et al. (2004) found that in the year before BCT, 60 % of alcoholic patients had been violent toward their female partner, five times the comparison sample rate of 12 %. In the year after BCT, IPV decreased significantly to 24 % of the alcoholic sample but remained higher than the comparison group. Among remitted alcoholics after BCT, IPV prevalence of 12 % was identical to the comparison sample. Results were similar for the second year after BCT. An earlier second study of male alcoholics (O'Farrell and Murphy 1995) found nearly identical results as the first study. A third study (Schumm et al. 2009) found an identical pattern of reduced IPV after BCT with female alcoholic patients.

These three studies show very substantial reductions in IPV in the first and second year after BCT. Using structural equation modeling, O'Farrell et al. (2004) found that these IPV reductions most likely result from BCT primary outcomes of reduced drinking and improved relationships. In other words, greater sobriety and better communication after BCT reduce IPV.

55.2.2.3 BCT and Child Adjustment Outcomes

Children living with a parent who abuses alcohol or other drugs often have significant emotional and behavioral problems. Kelley and Fals-Stewart (2002) conducted two studies (one in alcoholism, one in drug abuse) to find out whether BCT for a substance-abusing father, with its demonstrated reductions in domestic violence and reduced risk for family breakup, also has beneficial effects for the children in the family. Results were the same for children of male alcoholic and male drug-abusing fathers. BCT improved children's functioning in the year after the parents' treatment more than did individual-based treatment. Further, only BCT showed reduction in the number of children with clinically significant impairment. These results occurred even though the children themselves did not receive any treatment.

These two studies showing child functioning improves after parents undergo BCT raise the question of why might BCT be helpful to the couple's children. Parents who take part in BCT are not only improving their own relationship but also may be helping their children. Conceptually, BCT might have positive "trickle-down" effects on children because it has a positive impact on factors often associated with poor functioning among children who live with substance-abusing parents (i.e., parental substance use, partner violence, relationship conflict). Additionally, BCT methods to improve communication and reduce parental conflict are likely to make for a healthier home environment for children, ultimately leading to better children's adjustment.

55.2.3 International Considerations

Most of the research on BCT has been done in the USA. Four BCT studies have been done internationally outside the USA, in Canada, India, the Netherlands, and Australia.

55.2.3.1 Canada

O'Farrell et al. (2010) successfully transported a BCT program from Boston where it had been researched to a community clinic in Calgary. On-site BCT training in Calgary was followed by telephone consultations for 6 months. A quasi-experimental evaluation compared outcomes of (a) 38 alcoholic patients who received BCT plus treatment as usual (TAU) with (b) 33 alcoholic patients who received TAU only. The latter group was referred to the BCT program but did not enter it due to logistics or refusal. At baseline, the two groups were similar on demographics, substance use, relationship problems, and comorbid mood or anxiety diagnoses. At 6-month follow-up, patients treated in BCT, as compared to patients who got TAU only, were significantly more likely to be abstinent from alcohol and drugs and together rather than separated and to have higher relationship adjustment scores. Implementation of BCT was considered successful because BCT had better outcomes than individual-based TAU as expected from controlled trials of BCT and because the BCT program in Calgary continues to operate.

55.2.3.2 India

Nattala et al. (2010) randomized 90 male alcohol-dependent patients admitted for 3 weeks at an inpatient facility in Bangalore to either (a) dyadic relapse prevention (DRP), (b) individual relapse prevention (IRP), or (c) TAU. In DRP, which was based on BCT treatment manuals from the USA, both the patient and a family member (75 % spouses) planned and rehearsed how the dyad could work together to prevent relapse. IRP also focused on preventing relapse, but only the individual patient took part. Monthly follow-ups encouraged progress and collected outcome data for 6 months after leaving the treatment center. Results for this 6-month period showed that DRP performed better than IRP and TAU on quantity of alcohol consumed, drinking days, and family problems. The authors concluded that their study provided evidence for the effectiveness of Western-based family-oriented intervention for alcohol-dependent patients in India.

55.2.3.3 The Netherlands

Vedel et al. (2008) in Amsterdam randomized alcoholics to stand-alone BCT ($n = 30$; 10 90-min sessions) or individual cognitive- behavioral therapy (CBT; $n = 34$; 10 45–60-min sessions). Results showed both BCT and CBT significantly decreased drinking from before to after treatment, but BCT was not found to be significantly better than CBT (although a small to medium effect size favored BCT over CBT). Marital satisfaction of the spouse increased significantly after treatment in BCT but not in CBT, with a large effect size favoring BCT over CBT. At 6-month follow-up, BCT and CBT did not differ on drinking or marital outcomes.

Study authors concluded: "Stand-alone BCT is as effective as CBT in terms of reduced drinking and ... more effective in terms of enhancing relationship satisfaction. However, BCT is a more costly intervention, given that treatment sessions lasted almost twice as long as individual CBT sessions" (Vedel et al. 2008, p. 280). The suggestion that BCT is less cost-effective than CBT is based on the 90-min

BCT sessions used in this study, whereas many other studies have used 50–60-min BCT sessions (e.g., O'Farrell et al. 1998) the same as used for CBT.

55.2.3.4 Australia

Halford et al. (2001) in Brisbane randomly assigned 61 women whose husbands drank heavily but were not currently in alcohol treatment to BCT, supportive counseling, or stress management. All three treatments eased the wife's emotional distress, but neither BCT nor the other treatments improved the man's drinking or the couple's relationship. The lack of impact of BCT is not surprising when one considers that BCT has always been studied when the alcoholic has already sought help, not as a method for engaging treatment-resistant alcoholics. The 6 of 21 women assigned to BCT who actually engaged their husband in BCT completed this therapy and benefited from reduced drinking and happier relationships. This study suggests BCT may have limited usefulness when the alcoholic refuses to change or will not enter treatment with the spouse.

55.2.3.5 Other Countries

Results of these four small-scale studies of BCT outside the USA are encouraging. They show some initial ability to apply BCT and generally favorable outcomes. In addition, governments in other countries have recognized the favorable outcomes reported for BCT in the research literature and they have recommended that clinicians use BCT in treating addiction problems. For example, in the UK in 2008, BCT was one of only two therapeutic interventions which the National Institute of Clinical Excellence (NICE, the main UK body reviewing treatments that should be provided as part of the National Health Service) recommended for use in drug treatment services.

Despite the promise of BCT in countries that have developed health and addiction services, it seems unlikely that countries with less developed health systems would make use of BCT as currently practiced in the USA. Possibly, some components of BCT – such as the daily trust discussion in which the addicted person states their intention not to use that day to a family member who thanks the person for their efforts – might be adapted for use more broadly.

55.3 Conclusion

Behavioral Couples Therapy (BCT) is designed for married or cohabiting individuals seeking help for alcoholism or drug abuse. BCT aims to build support for abstinence and to improve relationship functioning. BCT promotes abstinence with a "recovery contract" that involves both members of the couple in a daily trust discussion ritual to reward abstinence. BCT improves the relationship with techniques for increasing positive activities and improving communication.

Research shows that BCT produces greater abstinence and better relationship functioning than typical individual-based treatment and reduces domestic violence and emotional problems of the couple's children. Most research on BCT has been done in the USA. Four BCT studies have been done internationally outside the USA, in Canada, India, the Netherlands, and Australia.

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Network Therapy in Addiction Treatment 56

Marc Galanter

Contents

Abstract

Individual therapists in office practice are often considered to have limited effectiveness in treating alcohol and drug dependence. In this chapter, the author describes network therapy, an approach developed to assure greater success in such treatment. A cognitive-behavioral model of addiction related to securing abstinence is reviewed by the role of social cohesiveness as a vehicle for engaging patients in treatment, along with a related technique for enhancing an addicted patient's commitment to the therapy. This is done by using the patient's family and peers as a therapeutic network to join the patient at intervals in therapy sessions.

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56.1 Introduction

This approach can be useful in addressing a broad range of addicted patients characterized by the following clinical hallmarks of addictive illness. When they initiate consumption of their addictive agent, be it alcohol, cocaine, opiates, or depressant drugs, they frequently cannot limit that consumption to a reasonable and predictable level; this phenomenon has been termed "loss of control" by clinicians who treat alcohol- or drug-dependent persons. Second, they consistently demonstrate relapse to the agent of abuse, that is, they attempted to stop using the drug for varying periods of time but returned to it, despite a specific intent to avoid it.

This treatment approach is not necessary for those abusers who can, in fact, learn to set limits on their use of alcohol or drugs; their abuse may be treated as a behavioral symptom in a more traditional psychotherapeutic fashion. Nor is it directed at those patients for whom the addictive pattern is most unmanageable (e.g., addicted people with unusual destabilizing circumstances such as homelessness, severe character pathology, or psychosis). These patients may need special supportive care (e.g., inpatient detoxification or long-term residential treatment).

56.2 Facets of Network Therapy

56.2.1 Key Elements of Network Therapy

Three elements are essential to the network therapy technique. The first is a cognitive-behavioral approach to relapse prevention, independently reported to be valuable in addiction treatment (Marlatt and Gordon 1985). Emphasis in this approach is placed on triggers to relapse and behavioral techniques for avoiding them, rather than on exploring underlying psychodynamic issues.

Second, support of the patient's natural social network is engaged in treatment. Peer support in AA has long been shown to be an effective vehicle for promoting abstinence, and the idea of the therapist's intervening with family and friends in starting treatment was employed in one of the early ambulatory techniques specific to addiction (Johnson 1986). The involvement of spouses (McCrady et al. 1991) has since been shown to be effective in enhancing the outcome of professional therapy.

Third, the orchestration of resources to provide community reinforcement suggests a more robust treatment intervention by providing a support for drug-free rehabilitation (Azrin et al. 1982). In this relation, Khantzian points to the "primary care therapist" as one who functions in direct coordinating and monitoring roles in order to combine psychotherapeutic and self-help elements (Khantzian 1988). It is this overall management role over circumstances outside as well as inside the office session that is presented to trainees to maximize the effectiveness of the intervention.

56.2.2 CBT and Social Support

Cognitive-Behavioral Therapy. This format for treatment has been shown to be effective for a wide variety of substance use disorders, including alcohol (Morgenstern and Longabaugh 2000), marijuana (Stephens et al. 2002), and cocaine dependence (Carroll 1998). It is premised on the original findings by Wikler (1973) on conditioning models of drug-seeking in heroin-addicted subjects.

The CBT approach is goal oriented and focuses on current circumstances in the patient's life. In network therapy, reference both in individual and conjoint sessions can be made to salient past experiences. CBT sessions are typically structured, so, for example, patients begin each network session with a recounting of recent events directly relevant to their addiction and recovery. This is followed by active participation and interaction of therapist, patient, and network members in response to the patient's report. CBT emphasizes psychoeducation in the context of relapse prevention, so that circumstances, thoughts, and interpersonal situations which have historically precipitated substance use are identified, and the patient (and network members as well) are taught to anticipate where such triggers can precipitate substance use.

The process of guided recall, noted previously, is particularly important because it allows the therapist both individual sessions with the patient alone and network sessions – in conjunction with network members along with the patient – to guide the patient to recognize a sequence of conditioned stimuli (triggers) which play a role in drug-seeking. Such triggers may not initially be apparent to the patient or network members but, with encouragement and prompting, can emerge over the course of an exploration of the circumstances which have led, either in the past, or in a recent "slip," to substance use.

56.2.2.1 Social Support

This issue has been studied in a variety of data sets in relation to the recovery from substance use disorders. For example, in the federal Project MATCH, three modalities, Twelve-Step facilitation, motivational enhancement, and cognitive-behavioral approaches, were compared. In a secondary analysis of findings from this multisite study, it was found (Zywiak and Wirtz 2002) that certain aspects of social support were most predictive of abstinence outcomes. Two social network characteristics that had a positive effect on outcome were the size of the supportive social network in the person's life and the number of members who were abstainers (or recovering alcoholics). I have found that nonproblem drinking participants are important to a long-term clinical outcome. As a matter of fact, a large number of network members, when their participation is effectively maintained over time, can counter a variety of circumstances that may undermine a patient's abstinence. Additionally, they can provide varied aspects of support relative to the patient's experience in recovery. And indeed, they should be free of substance-related problems. Of interest in this context, it has been reported that men are more typically encouraged by their wives to seek help, whereas women are more often encouraged by mothers, siblings, and children (Beckman and Amaro 1986).

56.2.2.2 Community Reinforcement

Family involvement in substance abuse treatment has long been shown to be effective in improving outcome, and there are numerous approaches that make use of social network involvement in treatment, including Behavioral Couples Therapy (Fals-Stewart et al. 2000), Marital Therapy (O'Farrell 1986), and the Community Reinforcement Approach (Azrin et al. 1982; Meyers et al. 2003).

More specifically, a Community Reinforcement and Family Training (CRAFT) Program includes many aspects of treatment that were employed in network therapy. The CRAFT approach was developed to encourage drinkers to enter therapy and reduce drinking, in part by eliciting support of concerned others as well as to enhance satisfaction with life among members of the patient's social network who were concerned about his or her drinking. As in network therapy, the CRAFT program includes a functional analysis of the patient's substance use, that is to say, understanding the substance use with respect to its antecedents and consequences. Like network therapy, it also serves to minimize reciprocal blaming and defensiveness among the concerned significant others and to promote a patient's sobriety-oriented activities.

In one large trial in which concerned significant others were randomized to one of three conditions, a comparison was made between Al-Anon-facilitated therapy, an approach similar to the Johnson Institute interventions, and the CRAFT model (Fuller et al. 1986). In that study, the CRAFT intervention was found to be more effective in engaging treatment-refusing, alcoholic subjects. Similar positive findings were obtained in studies on CRAFT with illicit drug users (Kirby et al. 1999; Meyers et al. 2002). On the other hand, in another study, concerned significant others were successfully trained to apply a modified Johnson Intervention technique in the absence of a therapist, and this approach was found to be successful in itself (Landau et al. 2004).

56.2.3 Starting a Network

Patients should be asked to bring their spouse or a close friend to the first session. Alcoholic patients often dislike certain things they hear when they first come for treatment and may deny or rationalize even if they voluntarily sought help. Because of their denial, a significant other is essential to both history taking and implementing a viable treatment plan. A close relative or spouse can often cut through the denial in a way that an unfamiliar therapist cannot and can therefore be invaluable in setting a standard of realism in dealing with the addiction.

Once the patient comes for an appointment, establishing a network is a task undertaken with active collaboration of patient and therapist. The two, aided by those parties who join the network initially, must search for the right balance of members. The therapist must carefully promote the choice of appropriate network members, however, just as the platoon leader selects those who will go into combat.

56.2.4 Defining the Network's Membership

The network will be crucial in determining the balance of the therapy. This process is not without problems, and the therapist must think in a strategic fashion of the interactions that may take place among network members. The following case illustrates the nature of their task.

A 25-year-old graduate student had been abusing cocaine since high school, in part drawing from funds from his affluent family, who lived in a remote city. At two points in the process of establishing his support network, the reactions of his live-in girlfriend, who worked with us from the outset, were particularly important. Both he and she agreed to bring in his 19-year-old sister, a freshman at a nearby college. He then mentioned a "friend" of his, apparently a woman whom he had apparently found attractive, even though there was no history of an overt romantic involvement. The expression on his girlfriend's face suggested that she did not like this idea, although she offered no rationale for excluding this potential rival. However, the idea of having to rely for assistance solely on two women who might see each other as competitors was unappealing. The therapist therefore finessed the idea of the "friend," and both she and the patient moved on to evaluating the patient's uncle, whom he initially preferred to exclude, despite the fact that his girlfriend thought him appropriate. It later turned out (as expected) that the uncle was perceived as a potentially disapproving representative of the parental generation. The therapist encouraged the patient to accept the uncle as a network member nonetheless, so as to round out the range of relationships within the group, and did spell out my rationale for his inclusion. The uncle did turn out to be caring and supportive, particularly after he was helped to understand the nature of the addictive process.

56.2.5 Defining the Network's Task

As conceived here, the therapist's relationship to the network is like that of a task-oriented team leader rather than that of a family therapist oriented toward insight. The network is established to implement a straightforward task: aiding the therapist in sustaining the patient's abstinence. It must be directed with the same clarity of purpose that a task force is directed in any effective organization. Competing and alternative goals must be suppressed or at least prevented from interfering with the primary task.

Unlike family members involved in traditional family therapy, network members are not led to expect symptom relief for themselves or self-realization. This lack of expectation prevents the development of competing goals for the network's meetings. It also provides the members protection from having their own motives scrutinized and thereby supports their continuing involvement without the threat of an assault on their psychological defenses. Because network members have – kindly – volunteered to participate, their motives must not be impugned. Their constructive behavior should be commended. It is useful to acknowledge

appreciation for the contribution they are making to the therapy. There is always a counterproductive tendency on their part to minimize the value of their contribution. The network must, therefore, be structured as an effective working group with high morale.

56.2.6 The Use of Twelve-Step Programs

Use of self-help modalities is desirable whenever possible. For the alcoholic, certainly, participation in Alcoholics Anonymous or Narcotics Anonymous is strongly encouraged. Groups such as Narcotics Anonymous, Pills Anonymous, and Cocaine Anonymous are modeled after AA and play a similarly useful role for drug abusers. One approach is to tell the patient that he or she is expected to attend at least two Twelve-Step meetings a week for at least 1 month, so as to become familiar with the program. If after a month the patient is quite reluctant to continue, and other aspects of the treatment are going well, the patient's nonparticipation may have to be accepted.

Some patients are more easily convinced to attend Twelve-Step meetings; others may be less compliant. The therapist should mobilize the support network as appropriate, so as to continue pressure for the patient's involvement with Twelve-Step groups for a reasonable trial. It may take a considerable period of time, but ultimately a patient may experience something of a conversion, wherein the patient adopts the group ethos and expresses a deep commitment to abstinence, a measure of commitment rarely observed in patients who undergo psychotherapy alone. When this occurs, the therapist may assume a more passive role in monitoring the patient's abstinence and keep an eye on the patient's ongoing involvement in a Twelve-Step program.

56.2.7 Use of Pharmacotherapy in the Network Format

For the alcoholic, medications like disulfiram or buprenorphine may be of marginal use in assuring abstinence when used in a traditional counseling context (Fuller et al. 1986) but becomes much more valuable when carefully integrated into work with the patient and network, particularly when the drug is taken under observation. A similar circumstance applies to the use of oral naltrexone for stabilizing abstinence in an opioid-dependent person. In the case of alcohol, it is a good idea to use the initial telephone contact to engage the patient's agreement to abstain from alcohol or drugs for the day immediately prior to the first session. The therapist then has the option of prescribing or administering medications at that time, or after an appropriate waiting time or detoxification. For a patient who is earnest about seeking assistance, this is often not difficult, if some time is spent on the phone making plans to avoid the drug context during that period. If it is not feasible to undertake this on the phone, it may be addressed in the first session. Such planning with the patient almost always involves organizing time with significant others and therefore serves as a basis for developing the patient's support network.

The administration of a medication under observation is a treatment option that is easily adapted to work with social networks. For example, a patient who takes disulfiram cannot drink; a patient who agrees to be observed by a responsible party while taking disulfiram will not miss his or her dose without the observer's knowing. This may take a measure of persuasion and, above all, the therapist's commitment that such an approach can be reasonable and helpful.

As noted previously, individual therapists traditionally have seen the addicted person as a patient with poor prognosis. This is largely because in the context of traditional psychotherapy, there are no behavioral controls to prevent the recurrence of drug use, and resources are not available for behavioral intervention if a recurrence takes place – which it usually does. A system of impediments to the emergence of relapse, resting heavily on the actual or symbolic role of the network, must therefore be established. The therapist must have assistance in addressing any minor episode of relapse so that this ever-present problem does not lead to an unmanageable relapse or an unsuccessful termination of therapy.

56.2.8 Format for Medication Observation by the Network

1. Take the medication every morning in front of a network member.
2. Take the pill so that that person can observe you swallowing them.
3. Have the observer write down the time of day the pills were taken on a list prepared by the therapist.
4. The observer brings the list in to the therapist's office at each network session.
5. The observer leaves a message on the therapist's answering machine on any day in which the patient had not taken the pills in a way that ingestion was not clearly observed.

56.2.9 Meeting Arrangements

At the outset of therapy, it is important to see the patient with the group on a weekly basis for at least the first month. Unstable circumstances demand more frequent contacts with the network. Sessions can be tapered off to biweekly and then to monthly intervals after a time.

To sustain the continuing commitment of the group, particularly that between the therapist and the network members, network sessions should be held every 3 months or so for the duration of the individual therapy. Once the patient has stabilized, the meetings tend less to address day-to-day issues. They may begin with the patient's recounting of the drug situation. Reflections on the patient's progress and goals, or sometimes on relations among the network members, then may be discussed. In any case, it is essential that network members contact the therapist if they are concerned about the patient's possible use of alcohol or drugs and that the therapist contact the network members if the therapist becomes concerned about a potential relapse.

56.2.10 Adapting Individual Therapy to the Network Treatment

Network sessions can be scheduled on a weekly basis at the outset of treatment. This is likely to compromise the number of individual contacts. Indeed, if sessions are held once a week, the patient may not be seen individually for a period of time. The patient may perceive this as a deprivation unless the individual therapy is presented as an opportunity for further growth predicated on achieving stable abstinence assured through work with the network.

When the individual therapy does begin, the traditional objectives of therapy must be arranged so as to accommodate the goals of the substance abuse treatment. For insight-oriented therapy, clarification of unconscious motivations is a primary objective; for supportive therapy, the bolstering of established constructive defenses is primary. In the therapeutic context that is described here, however, the following objectives are given precedence.

Of first importance is the need to address exposure to substances of abuse or exposure to cues that might precipitate alcohol or drug use (Galanter 1993). Both patient and therapist should be sensitive to this matter and explore these situations as they arise. Second, a stable social context in an appropriate social environment – one conducive to abstinence with minimal disruption of life circumstances – should be supported. Considerations of minor disruptions in place of residence, friends, or job need not be a primary issue for the patient with character disorder or neurosis, but they cannot go untended here. For a considerable period of time, the substance abuser is highly vulnerable to exacerbations of the addictive illness and in some respects must be viewed with the considerable caution with which one treats the recently compensated psychotic.

Finally, after these priorities have been attended to, psychological conflicts that the patient must resolve, relative to his or her own growth, are considered. As the therapy continues, these come to assume a more prominent role. In the earlier phases, they are likely to reflect directly issues associated with previous drug use. Later, however, as the issue of addiction becomes less compelling from day to day, the context of the treatment increasingly will come to resemble the traditional psychotherapeutic context. Given the optimism generated by an initial victory over the addictive process, the patient will be in an excellent position to move forward in therapy with a positive view of his or her future.

56.2.11 The Technique

56.2.11.1 Start a Network as Soon as Possible

1. It is important to see the alcohol or drug abuser promptly, because the window of opportunity for openness to treatment is generally brief. A week's delay can result in a person's reverting back to drunkenness or losing motivation.
2. If the person is married, engage the spouse early on, preferably at the time of the first phone call. Point out that addiction is a family problem. For most drugs, you can enlist the spouse in assuring that the patient arrives at your office with a day's sobriety.

3. In the initial interview, frame the exchange so that a good case is built for the grave consequences of the patient's addiction, and do this before the patient can introduce his or her system of denial. That way you are not putting the spouse or other network members in the awkward position of having to contradict a close relation.
4. Then make clear that the patient needs to be abstinent, starting now. (A tapered detoxification may be necessary sometimes, as with depressant pills.)
5. When seeing an alcoholic patient for the first time, start the patient on disulfiram treatment as soon as possible, in the office if you can. Have the patient continue taking disulfiram under observation of a network member.
6. Start arranging for a network to be assembled at the first session, generally involving a number of the patient's family or close friends.
7. From the very first meeting you should consider how to ensure sobriety till the next meeting, and plan that with the network. Initially, their immediate company, a plan for daily AA attendance, and planned activities may all be necessary.

56.2.11.2 Manage the Network with Care

1. Include people who are close to the patient, have a long-standing relationship with the patient, and are trusted. Avoid members with substance problems, because they will let you down when you need their unbiased support. Avoid superiors and subordinates at work, because they have an overriding relationship with the patient independent of friendship.
2. Get a balanced group. Avoid a network composed solely of the parental generation, or of younger people, or of people of the opposite sex. Sometimes a nascent network selects itself for a consultation if the patient is reluctant to address his or her own problem. Such a group will later supportively engage the patient in the network, with your careful guidance.
3. Make sure that the mood of meetings is trusting and free of recrimination. Avoid letting the patient or the network members feel guilty or angry in meetings. Explain issues of conflict in terms of the problems presented by addiction; do not get into personality conflicts.
4. The tone should be directive. That is to say, give explicit instructions to support and ensure abstinence. A feeling of teamwork should be promoted, with no psychologizing or impugning members' motives.
5. Meet as frequently as necessary to ensure abstinence, perhaps once a week for a month, every other week for the next few months, and every month or two by the end of a year.
6. The network should have no agenda other than to support the patient's abstinence. But as abstinence is stabilized, the network can help the patient plan for a new drug-free adaptation. It is not there to work on family relations or help other members with their problems, although it may do this indirectly.

56.2.11.3 Keep the Network's Agenda Focused

1. Maintaining abstinence. The patient and the network members should report at the outset of each session any exposure of the patient to alcohol and drugs. The patient and network members should be instructed on the nature of relapse and plan with the therapist how to sustain abstinence. Cues to conditioned drug-seeking should be examined.
2. Supporting the network's integrity. Everyone has a role in this. The patient is expected to make sure that network members keep their meeting appointments and stay involved with the treatment. The therapist sets meeting times and summons the network for any emergency, such as relapse; the therapist does whatever is necessary to secure stability of the membership if the patient is having trouble doing so. Network members' responsibility is to attend network sessions, although they may be asked to undertake other supportive activity with the patient.
3. Securing future behavior. The therapist should combine any and all modalities necessary to ensure the patient's stability, such as a stable, drug-free residence; the avoidance of substance-abusing friends; attendance at Twelve-Step meetings; medications such as disulfiram or blocking agents; observed urinalysis; and ancillary psychiatric care. Written agreements may be handy, such as a mutually acceptable contingency contract with penalties for violation of understandings.

56.2.11.4 Make Use of Alcoholics Anonymous and Other Self-Help Groups

1. Patients should be expected to go to meetings of AA or related groups at least two to three times, with follow-up discussion in therapy.
2. If patients have reservations about these meetings, try to help them understand how to deal with those reservations. Issues such as social anxiety should be explored if they make a patient reluctant to participate. Generally, resistance to Twelve-Step groups can be related to other areas of inhibition in a person's life, as well as to the denial of addiction.
3. As with other spiritual involvements, do not probe the patients' motivation or commitment to Twelve-Step groups once engaged. Allow them to work out things on their own, but be prepared to listen.

56.2.11.5 Cultural Issues

The adaptability of network therapy in different countries is delimited by cultural and economic issues. For example, in national settings where shame is a predominant motivating factor, it is important for the clinician to be attentive to the potential for reluctance on the part of family members to acknowledge a substance abuser's problem. Often, they will be concerned that members of their community would look down on the entire family because of the addiction in one of its members. It would be important to point out to family members that the resolution of the patient's problem provides as an opportunity for resecuring the tarnished status of the family in their community.

Another issue relates to economic concerns. In many clinical settings patients have limited contact with their respective families, or even with drug-free peers. In such circumstances, a network is frequently established among patients in the treatment setting itself, so that mutual support can be elicited once a treatment community has been well established, be it a clinic, residence, or therapeutic community. It is for this reason that indigent patients are best treated in settings where there is an active promotion of mutuality and peer support.

56.2.12 Research on Network Therapy

56.2.12.1 Study on Training Naïve Therapists

A course of training for psychiatric residents naive to addiction and ambulatory treatments was undertaken over a period of 2 academic years. Before beginning treatment, the residents were given a structured treatment manual for network therapy and participated in a 13-session seminar on application of the network therapy technique. Cocaine-abusing patients were eligible for treatment in this study if they could come for evaluation with a friend or family member who could participate in their treatment. In all, 22 patients were enrolled. The treating psychiatric residents were able to establish requisite networks for 20 of these patients (i.e., a network with at least one member). The networks had an average of 2.3 members, and the most typical configuration included family members and friends. Supervisors' evaluation of videotapes of the network sessions employing standardized instruments indicated good adherence to the manualized treatment, with effective use of network therapy techniques. The outcome of treatment (Galanter et al. 1997; Keller et al. 1997; Galanter et al. 2002) reflected retention and abstinence rates as good as, or better than, comparable ambulatory care carried out by therapists experienced in addiction treatment. The study demonstrated the feasibility of teaching the network technique to therapists naive to addiction treatment.

Galanter et al. (2004) evaluated the impact of network therapy relative to a control condition (medical management, MM) among 66 patients who were inducted onto buprenorphine for 16 weeks and then tapered to zero dose. Network therapy resulted in a greater percentage of opioid-free urines than did MM (65 % vs. 45 %). By the end of treatment, network therapy patients were more likely to experience a positive outcome relative to secondary heroin use (50 % vs. 23 %). The use of network therapy in office practice may enhance the effectiveness of eliminating secondary heroin use during buprenorphine maintenance.

56.2.12.2 Adaptations of Network Therapy Treatment

Rothenberg et al. (2002) adapted NT and combined it with relapse prevention and a voucher reinforcement system in the treatment of opioid-dependent patients who were enrolled in a 6-month course of treatment with naltrexone referred to as behavioral naltrexone therapy (BNT). The NT component involved one significant other who could monitor adherence to naltrexone. In addition to the patient

receiving vouchers for each day of abstinence and each pill taken, the network member was reinforced with a voucher for each pill recorded as monitored. The primary treatment outcome was retention in treatment. Patients who used methadone at baseline did more poorly than those using only heroin as demonstrated in the retention rates: 39 % versus 65 % and 0 % versus 31 %, respectively, at 1 month and 6 months.

Copello et al. (2002) combined elements of NT with social aspects of the community reinforcement approach and relapse prevention referred to as social behavior and network therapy (SBNT) in the treatment of persons with alcohol-drinking problems. A number of social skills training strategies are incorporated into the treatment especially those involving social competence in relation to the development of positive social support for change in alcohol use. Every individual involved in treatment is considered a client in his/her own right and the person with alcohol problems is referred to as the focal client. The core element of the approach is mobilizing the support of the network even though this may involve network sessions that are conducted in the absence of the focal client. In their initial feasibility study with 33 clients, there were two cases in which sessions were held with network members in the absence of the focal client and in both cases reengagement of the focal client in treatment was achieved. Out of the 33 clients enrolled in the study, 23 formed a network with the mean number of network members = 1.82 and the mean number of network sessions = 5.24. In a multisite, randomized, controlled trial of 742 clients with alcohol problems, the UKATT Research Team (2005a) compared SBNT to motivational enhancement therapy (MET). Both treatment groups exhibited similar reductions in alcohol consumption and alcohol-related problems and improvement in mental functioning over a 12-month period. Attending more sessions was associated with a better outcome, and SBNT patients with greater motivation to change and those with more negative short-term expectancies were more likely to attend (Dale et al. 2011).

Additional studies involving the UKATT study sample were conducted assessing (1) cost-effectiveness (UKATT Research Team 2005b), (2) client-treatment matching effects (UKATT Research Team 2008), (3) clients' perceptions of change in alcohol-drinking behaviors (Orford et al. 2009), and drinking goal preference (Adamson et al. 2010). The UKATT Research Team evaluated the cost-effectiveness of SBNT relative to motivational enhancement therapy. SBNT resulted in a fivefold cost savings in health, social, and criminal justice service expenditures and was similar to cost-effectiveness estimates obtained for motivational enhancement therapy. The UKATT Research Team (2008) tested a priori hypotheses concerning client-treatment matching effects similar to those tested in Project MATCH. The findings were consistent with Project MATCH in that no hypothesized matching effects were significant. Orford et al. (2009) interviewed a subset of clients (n = 397) who participated in this trial to assess their views concerning whether any positive changes in drinking behavior had occurred and to what they attributed those changes. . . At 3 months after randomization to treatment, SBNT clients made more social attributions (e.g., involvement of others in supporting behavior change) and MET clients made more motivational attributions

(e.g., awareness of the consequences of drinking.) Patients who initially stated a preference for abstinence showed a better outcome than those stating a preference for non-abstinence. This was true both at 3-month and 12-month follow-up (Adamson et al. 2010).

Copello et al. (2006) adapted SBNT for persons presenting with drug problems. Of 31 clients enrolled in the study, 23 received SBNT and had outcomes data available at 3-month follow-up. Reductions in the amount of heroin used per day and increases in family cohesion and family satisfaction were documented. Open-ended interviews with clients, network members, and therapists were conducted in a qualitative investigation of respondents' perceptions of SBNT (49). Major themes that emerged from analysis of the interview responses included the value of SBNT in (1) increasing network support for reducing drug use, (2) promoting open and honest communication between clients and network members about drug use, and (3) increasing network members' understanding of drugs and the focal person's behavior. Williamson et al. (2007) suggest that these features of SBNT may be more prominent when the problem is one of illicit drug use than when the problem involves alcohol use.

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CRA and CRAFT: Behavioural Treatments for Both Motivated and Unmotivated Substance Abusing Individuals

57

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Contents

Abstract

The Community Reinforcement Approach (CRA) is a behavioral treatment for substance abuse problems which is based on the belief that a nondrinking and nonusing lifestyle must be accessible and experienced as rewarding in order for individuals to choose it routinely over substance use. As part of CRA, the client's "community" (e.g., family, friends, colleagues, organizations, work) is explored to find new areas of potential reinforcement that can compete with substance use. CRA therapists help clients determine which goals they want to pursue in life, and they then teach clients the skills required to obtain these goals. Community Reinforcement and Family Training (CRAFT) is a treatment for the family members or close friends (Concerned Significant Others, CSOs) of unmotivated, treatment-refusing substance abusers (identified patients, IPs). CRAFT therapists work with CSOs in an attempt to change the home

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environment of the unmotivated IPs such that a healthy and enjoyable lifestyle is supported over one dominated by substance use. CRAFT goals include getting IPs to seek treatment but also having CSOs take care of themselves as well. Both CRA and CRAFT have solid empirical support, and each has been used successfully with diverse populations and various drugs of choice.

57.1 Introduction

The Community Reinforcement Approach (CRA) and Community Reinforcement and Family Training (CRAFT) are behavioral treatments based on the belief that the lives of individuals with substance abuse problems will only become and remain healthy if clean/sober behavior that is experienced as rewarding becomes a routine part of their lives. Clinicians work directly with the people with the substance abuse problems in CRA, and thus, it is the clinicians' job to help those clients identify and sample healthier lifestyles. In the case of CRAFT, clinicians must work through family members to identify and support these rewarding behaviors, because the substance-abusing individuals refuse to seek treatment initially. Both CRA and CRAFT have solid empirical support overall, and each has been used successfully with diverse populations and various drugs of choice.

57.2 Understanding and Using CRA and CRAFT

57.2.1 CRA Procedures

57.2.1.1 CRA Functional Analyses

In order to better understand the events that lead to substance use, as well as the positive and negative consequences that follow, a clinician often first conducts a functional analysis (F.A.) of substance-using behavior. The F.A. is a semi-structured interview which highlights the fact that substance use does not occur at random, but instead is preceded by certain events (i.e., antecedents/triggers) and followed by certain consequences. During the F.A., the clinician first works with the client to identify external (people, places, times) and internal (thoughts, feelings) triggers. Later in therapy, this information can be helpful when learning how to alter or effectively cope with triggers that have led to substance use in the past. The second part of the F.A. involves the clinician gathering more information about how the substance of choice is used, such as how much is consumed and over what period of time. These details can be useful in quantitatively gauging progress as therapy proceeds.

Finally, the clinician uses the F.A. to explore the positive and negative consequences that occur after engaging in substance use. Although it may be tempting for clinicians to focus exclusively on the negative consequences, outlining and discussing the positive consequences is vital because they represent the motives

that *sustain* the substance use behavior. For example, a client may state that he enjoys drinking because it allows him to relax and have fun with friends after a stressful day at work. Once these positive consequences are identified, the clinician can help the client generate reasonable alternatives for relaxing and having fun after work: options that do not involve alcohol. The positive consequences of substance use are referred to as short term, while the negative consequences are specified as long term. The latter are broken down into multiple domains: interpersonal, physical, emotional, legal, job, and financial.

The CRA program's second type of F.A. is for prosocial behaviors (e.g., going for a bike ride, relaxing at a coffee shop). A better understanding of the antecedents and consequences surrounding these behaviors helps the clinician see why a prosocial behavior is sometimes chosen over a substance-using one (and vice versa) and identify possible mechanisms for getting the client to select the healthy alternative more often.

57.2.1.2 Sobriety Sampling

Sobriety sampling is a procedure that clinicians use to get clients to agree to "sample" a time-limited period of sobriety. This "trial period" of sobriety feels much more attainable for clients and therefore receives less resistance than a demand for an immediate, indefinite, abstinence commitment. Sobriety sampling is used regardless of whether the final treatment goal is abstinence or moderation. If the goal is abstinence, small, manageable periods of sobriety are linked together over time. If the client hopes to become a moderate drinker/substance user, the clinician still asks for the client to at least start treatment by sampling a period of sobriety. Some of the benefits of sobriety sampling, which are discussed with the client, include providing an opportunity to break old behavior patterns, allowing for experimentation with new coping strategies, and increasing self-efficacy through goal attainment.

Once the client has agreed to sample sobriety, the negotiation over the length of the trial period begins. Frequently the clinician suggests a relatively long period of abstinence, such as 90 days. The client's motivators for abstinence are linked to the goal. For example, a clinician might reason, "Your ex-wife said she won't allow you anywhere near your daughter if you haven't demonstrated that you can be sober for a period of time. You mentioned that your daughter's kindergarten "graduation" is in 2 months and that you'd love to attend it. That might be a good reason to shoot for 2 months of sobriety. What do you think?" If the client is unwilling or feels unable to agree to the suggested period of sobriety, the clinician will negotiate with the client to reach a mutually agreed upon goal.

The final part of sobriety sampling entails setting up a plan such that the client can actively work to achieve the goal. Using information collected during the F.A. for substance use, the client is encouraged to identify alternatives to substance use and to develop plans for handling common triggers. It is often helpful to identify and problem solve any upcoming high-risk situations and to develop specific backup plans.

57.2.1.3 The Treatment Plan: Happiness Scale and Goals of Counseling

The two main tools utilized as part of the CRA treatment plan include the Happiness Scale and the Goals of Counseling form. The Happiness Scale is a 10-item questionnaire that asks clients to rate their happiness on a 10-point scale (where 10 indicates "completely happy") in each of the following areas: substance use, job or educational progress, money management, social life, personal habits, marriage/family relationships, legal issues, emotional life, communication, and general happiness (Meyers and Smith 1995). Information regarding the client's happiness in each of these domains helps set the stage for developing the goals of treatment. For example, the clinician might say, "I see that you've rated your 'social life' a '4.' What would have to change in order for you to be able to rate your 'social life' a '5' or '6'?" The Happiness Scale also can be readministered throughout therapy to track progress in specific domains.

The same ten domains from the Happiness Scale are outlined on the Goals of Counseling form, where the clinician works with the client to set goals that are positive (what the client *wants* as opposed to what he/she does not want anymore), specific, measurable, realistic, and under the client's control. In addition to setting specific goals, the clinician and client work together to identify the necessary steps needed to accomplish each goal. A representative *goal* in the social life area might be to meet a new nonusing person and go for coffee with him/her once in the next month. The initial *steps* toward attaining that goal might be to search the Internet to find out which coffee shops look inviting and then to visit two of the shops in the upcoming week. These weekly steps toward a goal are essentially the homework assignment. Importantly, the clinician checks on progress toward completing the homework weekly and discusses any barriers that have appeared.

Incorporating goals to improve various areas of the client's life is fundamental to the CRA approach, given that the overall objective is to increase sources of substance-free reinforcement in the client's life. Many of these goals, and the strategies (steps) for attaining them, require specific behavioral skills training. The CRA program offers skills training in such areas as communication, problem solving, and drink/drug refusal.

57.2.1.4 Communication Skills

CRA emphasizes the importance of positive communication training as a component of treatment, in part because many individuals who abuse substances report that problematic interactions serve as relapse triggers. Furthermore, effective communication paves the way for the successful implementation of a variety of goal-related tasks, such as interviewing for jobs, asking teachers for extra help, and talking with a partner about relationship struggles. CRA first discusses the rationale for focusing on communication training and then offers clients three communication guidelines for starting a difficult conversation: (1) give an understanding statement, (2) take partial responsibility, and (3) offer to help. Assume, for example, that an adolescent female has been wrongly accused of cheating on a test and has been given detention for a week. The clinician would work with the client to develop the beginning of a conversation with the teacher that sounded somewhat

similar to: "Mrs. Gray, I can see why you thought I was cheating in class yesterday when you heard whispering coming from the back of the room during the test, because I've had trouble with cheating in the past (*understanding statement*). And I know it didn't help for me to get all upset as soon as you started talking to me; I guess it sort of made me seem guilty (*partial responsibility statement*). What can I do to convince you that things are different now and that I don't cheat anymore?" (*offer to help*).

Clients report that when they start a conversation with these communication components they typically are met with less defensiveness from the listener. The message being conveyed is that more than one person contributes to interpersonal problems, and the communicator is willing to take an active role in improving the situation. Clinicians teach these skills by providing relevant examples and engaging the client in role plays complete with specific feedback.

57.2.1.5 Problem-Solving Skills

Given that individuals who abuse substances frequently report using alcohol or drugs as their problem-solving, stress-reduction strategies, CRA includes a problem-solving skills training module. CRA's approach to problem solving, which is based on the work by D'Zurilla and Goldfried (1971), outlines seven main steps: (1) narrowly define the problem, (2) generate potential solutions (brainstorm), (3) eliminate undesired suggestions, (4) select one potential solution, (5) generate possible obstacles, (6) address these obstacles, and (7) assign the specific task (i.e., the homework). As with all homework assignments, the clinician carefully evaluates the outcome of the task at the start of the next therapy session.

This problem-solving procedure allows clients to break down problems into manageable steps, to think creatively about possible solutions, and to realistically assess the likelihood that the proposed solution will work. Once clients have put their proposed solution into action, they are taught to critically evaluate the outcome. If the proposed solution did not meet their needs, they are encouraged either to modify the attempted solution or to select a different solution generated during step #2. Some of the common types of problems for which this exercise is conducted include handling cravings, finding a fun and healthy social activity for a weekend night, and improving study or sleep habits.

57.2.1.6 Drink and Drug Refusal Skills

A critical component of relapse prevention entails having the communication skills to successfully refuse offers of alcohol or drugs. This set of CRA skills can be organized into three domains: (1) learning how to get social support when sobriety is threatened, (2) anticipating and preparing for high-risk situations, and (3) practicing the assertive refusal of invitations to use substances. Social reinforcement often plays a large role in determining behavior. Based on this premise, CRA encourages clients to create social environments that are supportive of sobriety. Clients often benefit from role-playing conversations they hope to have with family members and friends about their desire to sample abstinence and their need for support.

Information gathered during the F.A. can be extremely useful when helping the client identify high-risk situations. Working with personally relevant situations will make the drink/drug refusal role plays more effective. Oftentimes clients are overly confident that they will be able to walk into these situations and "simply not drink" (or use other substances). Despite this confidence, refusal is often much more difficult than anticipated, and thus, clients are encouraged to practice refusing offers assertively.

Without this specialized assertiveness training, clients tend to respond either too passively or too aggressively to substance use offers. Suggested components of an assertive response include (1) saying "no, thanks" without feeling guilty, (2) using appropriate body language (good eye contact, a firm stance, etc.), (3) suggesting alternatives ("No, thanks, but I'll take a soda"), (4) changing the subject ("Did you see that game last night? Unbelievable!"), (5) directly addressing the aggressor about the issue if needed ("I've already said more than once that I'm not smoking. Why is it important to you that I smoke?"), and (6) leaving the situation. Clients are asked to generate their own assertive response style and are coached in its implementation.

57.2.1.7 Job-Finding Skills

CRA incorporates training in a wide variety of skills so that clients are able to utilize social, recreational, familial, and vocational forms of reinforcement to create a more rewarding substance-free lifestyle. Suitable employment can be an excellent source of healthy reinforcement, as it can provide a boost to self-esteem, enjoyable social relationships, and money. Relying heavily on the work outlined by Azrin and Besalel in their *Job Club Counselor's Manual* (1980), CRA offers a step-by-step approach to obtaining a satisfying job and keeping it. The procedure begins by asking clients to carefully consider the types of jobs for which they are best suited, such as ones that are unlikely to contribute to relapse. A system is then established for tracking contacts with potential employers. Clients are assisted with developing résumés and completing job applications in a manner that highlights their strengths. Extensive practice is provided in calling potential employers and going on job interviews. With respect to keeping a job, clinicians help clients anticipate difficult work situations based on previous job problems, and problem-solving skills are used to generate potential solutions.

57.2.1.8 Social/Recreational Counseling

Another primary source of substance-free reinforcement comes from social/recreational activities. Prior to treatment, clients' social and recreational environments are strongly associated with substance use, and consequently identifying enjoyable substance-free social activities often is a difficult task. Importantly, clinicians are careful not to impose their own values as to what constitutes a fun recreational activity, and furthermore they attempt to identify at least some activities that occur during high-risk times (e.g., weekends, evenings) and thereby directly compete with substance use. CRA offers several approaches for developing ideas about

healthy social activities, including the use of problem solving. Once an activity is identified, a homework assignment is made to sample the activity, and as usual, potential barriers (e.g., transportation, money, fear of rejection) are discussed.

Periodically clinicians are doubtful that a client will follow through and sample a new activity despite being motivated to do so. In these cases clinicians utilize a technique, *systematic encouragement*, to increase the likelihood that the client will successfully complete that homework assignment in the upcoming week. Systematic encouragement involves helping the client take the first step toward engaging in the new activity before leaving the session. For example, assume a client is interested in playing basketball at the local YMCA but appears unlikely to make any progress toward pursuing that goal without assistance. The clinician either would help the client search for relevant information on the YMCA website (e.g., the YMCA's operation schedule, whether there are "pickup" games on the basketball court, whether fees are involved) or would conduct a role play in which the client practiced calling the organization to ask these questions directly. Next, a specific plan for getting to the YMCA would be created, and obstacles would be addressed. The clinician would start the next session by reviewing the client's experience at the YMCA, in part to determine the reinforcement value.

57.2.1.9 Relapse Prevention

CRA recognizes the importance of preparing clients for high-risk situations in an effort to prevent a relapse, and helping clients get back on track quickly if a relapse occurs. The initial F.A. is revisited in an effort to prevent an impending relapse, since it already has outlined the antecedents and consequences that surround typical drinking/using situations. In the event that a relapse has occurred, the F.A. is readministered with a focus on the specific relapse episode. The clinician takes a solution-oriented approach to highlighting what triggered the relapse and to identifying alternatives to substance use in that particular situation.

CRA clinicians also borrow from the relapse literature more generally when they draw and label a "chain" to illustrate the events that led to the relapse. At first, clients usually only identify one poor decision that led to their use, but in reality there are a number of small and seemingly unrelated decisions throughout the day that led down that path. With the behavioral chain laid out, clients see that they had the option to change the outcome by making a different decision at multiple points along the chain. Clinicians emphasize the fact that it is much easier to change the course earlier as compared to later in the chain of events.

CRA relapse prevention also includes the Early Warning System, which entails clients setting up a plan for enlisting the support of a concerned family member or friend in the event that a relapse appears imminent. The clinician helps the client both identify an individual who will be available and supportive at an extremely high-risk time and determine precisely what the client would want the individual to do on such an occasion. Finally, the client rehearses the conversation that will take place with the support person and commits to having that conversation as part of the weekly homework.

57.2.1.10 Medication Monitoring

CRA has a medication monitoring procedure that is used with clients who have difficulty taking their prescribed medication. The procedure originally was developed for clients who were taking disulfiram (Antabuse), a medication that causes individuals to get very ill if they ingest alcohol. This "deterrent" to drinking is sometimes introduced to clients who repeatedly are unsuccessful at achieving even short periods of abstinence or who face serious consequences if they drink. But in order for disulfiram to be effective, it must be taken several days per week, and therefore, it is important to incorporate a medication monitoring component. The "monitor," a concerned individual who has daily contact with the client, attends a session with the client in order to learn positive communication skills for administering the disulfiram. For example, the monitor rehearses a conversation such as, "Thank you for taking your pill today. I know this hasn't been easy, but this shows how much you care about our family." In addition to teaching the monitor to express support and appreciation for the client's efforts, a plan is developed (with the client's consent) regarding the steps to take if the client refuses to take his or her medication (e.g., call the therapist). Medication monitoring can be incorporated into the Early Warning System, because if clients are refusing to take their medication, it is often a warning sign of an upcoming relapse. Although initially introduced to monitor disulfiram administration, more recently the medication monitoring procedure has been used to monitor a variety of other kinds of medication, such as for attention deficit hyperactivity disorder (ADHD) and depression.

57.2.1.11 Relationship Therapy

For clients involved in a romantic relationship, improving interactions with the partner can be another powerful source of reinforcement. CRA's relationship therapy focuses on improving communication and problem-solving skills and setting/negotiating reasonable goals. The couple begins by completing the Relationship Happiness Scale, a tool similar to the original Happiness Scale. However, each individual rates his/her happiness *with the partner* on a 10-point scale across ten domains: household responsibilities, raising the children, social activities, money management, communication, sex and affection, job or school, emotional support, partner's independence, and general happiness. Similar to the Goals of Counseling, each partner formulates and writes down what he/she would like the partner to do in several of the ten domains. The partners are coached to state their requests in positive, specific, and measurable terms and then are taught to use positive communication skills to make the request verbally. Homework assignments are made to tackle the negotiated goals. As part of the "Daily Reminder to be Nice" exercise, each partner commits to increasing at least one of seven partner-pleasing behaviors (e.g., expressing appreciation, giving a pleasant surprise) on a daily basis in an effort to reinstate positive behaviors that were more frequent at the beginning of the relationship, but dwindled over time. In subsequent sessions the partners report on any barriers to completing their goals for the week and identify future goals.

57.2.1.12 Caregiver Procedures

When the substance-using client is an adolescent, the adolescent version of CRA (A-CRA) is used (see Godley et al. 2001). For the most part this entails relying on age-modified questionnaires and procedures and the inclusion of sessions for the caregivers (e.g., parents, grandparents), both alone and with the adolescent client. The sessions with just the caregiver(s) are devoted to describing basic parenting practices that support the adolescent's sobriety and to teaching CRA communication and problem-solving skills. The sessions that include the adolescent are similar in structure to the relationship therapy sessions, in that they focus on negotiating goals for the caregivers and the adolescent client, as well as establishing clear strategies for obtaining the goals. Positive communication and problem-solving skills are stressed throughout.

57.2.2 CRA Scientific Support

For the past 40 years, the Community Reinforcement Approach (CRA) has been accruing evidence of its efficacy and effectiveness in treating alcohol and drug problems. The earliest CRA studies were conducted with inpatients on alcohol wards (Azrin 1976; Hunt and Azrin 1973). In both of these small studies, CRA was shown to be significantly better than standard treatment, which at the time was participation in a hospital's Alcoholics Anonymous program. Specifically, at the 6-month follow-up, the participants in the CRA program had fewer days of drinking and institutionalization and more days working compared to those in standard treatment. The second of these studies introduced several new procedures to the original CRA protocol, most notably a disulfiram (Antabuse) compliance monitoring program (Azrin 1976).

The third CRA study was the first to use an outpatient population of problem drinkers (Azrin et al. 1982). The researchers contrasted three treatments: traditional (12-step) treatment with a disulfiram prescription, traditional treatment with the disulfiram compliance program, and CRA with the disulfiram compliance program. The compliance program included not only monitoring of the daily disulfiram use by a loved one but training in positive communication skills as well. As expected, the conditions that included the disulfiram compliance component had the highest abstinence rates, with the CRA program outperforming the traditional program overall at 6 months.

A much larger study ($N = 237$) with an ethnically diverse population was conducted which extended the design of the first outpatient study by examining whether one's willingness to take disulfiram affected the findings (Miller et al. 2001). Although the study revealed less robust results, CRA still showed an advantage over traditional treatment on several outcome measures. The CRA program was modified in another study to make it applicable to a day treatment program for homeless alcohol-dependent individuals (Smith et al. 1998). As predicted, CRA (conducted in group format) was proven

to be more effective than the standard treatment offered at that particular homeless shelter in terms of drinking outcomes.

Although originally developed as a treatment for individuals with alcohol problems, CRA has proven to be promising for other types of substance use, including cocaine (Azrin et al. 1996), tobacco (Roozen et al. 2006), and opioids (e.g., Abbott et al. 1998; Bickel et al. 1997; Roozen et al. 2003). One of the newer studies determined that a computerized version of CRA for opioid-dependent individuals (on buprenorphine maintenance) did as well as a therapist-delivered version of CRA, both of which did significantly better than standard treatment (Bickel et al. 2008). Over the years a series of studies have examined cocaine-dependent individuals treated with a combination of CRA and contingency management (vouchers) for clean urines and found highly favorable results when contrasted with standard treatment (e.g., Garcia-Rodriguez et al. 2009; see Higgins and Abbott 2001). In an effort to identify patterns among CRA study results, Roozen and colleagues conducted a systematic review of 11 randomized controlled trials. They discovered strong evidence that CRA was more effective than usual care when considering the number of drinking days. Furthermore, there was strong evidence that CRA with vouchers was more effective than usual care in achieving cocaine abstinence and more effective than CRA alone. However, there was evidence that the effect of the vouchers dissipated over time after their discontinuation (Roozen et al. 2004). Interestingly, one study determined that the CRA component of the therapy package improved alcohol and employment outcomes compared to vouchers alone in cocaine-addicted individuals (Higgins et al. 2003).

In more recent years CRA has been applied to adolescent populations, most notably as part of the national Cannabis Youth Treatment Study. Similar to the other treatments, adolescent CRA (A-CRA) demonstrated significant pre-post improvements in days of abstinence and days in recovery (i.e., no substance use problems and not institutionalized) and was the most cost-effective treatment within its trial of the study (Dennis et al. 2004). When homeless, runaway youths attending a drop-in center were randomly assigned to CRA or treatment as usual, the CRA participants demonstrated significantly greater improvements in substance use, depression, and social stability (Slesnick et al. 2007). Early results from one multi-site study with over 2,000 adolescents showed that A-CRA was equally effective across ethnic groups (Godley et al. 2011).

57.2.3 International Considerations

CRA has gained international recognition in more recent years. For instance, CRA was implemented successfully within Spain's Public Health System with cocaine-dependent individuals in an outpatient clinic (Secades-Villa et al. 2011). A later study added vouchers to the CRA program and improved treatment outcomes (Garcia-Fernandez et al. 2011). Several Dutch studies and reviews led by Roozen and colleagues already have been noted (e.g., Roozen et al. 2003, 2004, 2006), and a pilot study of CRA with substance-abusing individuals in Mexico detected highly

promising findings (Torres et al. 2005). Finally, the National Drugs Strategy of Ireland has acknowledged CRA as an effective evidence-based approach that can be used as an adjunct to services delivered within the rehabilitation pillar, and Germany has already sponsored a CRA conference. To date, the CRA trainers' manual, *Clinical Guide to Alcohol Treatment*: *The Community Reinforcement Approach* (Meyers and Smith 1995), has been translated into German and Dutch.

57.2.4 CRAFT Procedures

57.2.4.1 Enhancement of the Concerned Significant Other's Motivation

CRAFT begins by enhancing the motivation of the concerned significant other (CSO), the *non*-substance-abusing person who is seeking treatment in an effort to get help for a treatment-refusing loved one who is abusing substances (identified patient, IP). CSOs are told that they can play a pivotal role in helping their family member engage in treatment, in part because they have a wealth of knowledge about the IP's substance use, and the degree of contact between the CSO and IP allows the CSO to make powerful changes in the IP's environment. To start the session, clinicians first ask CSOs to describe the negative consequences they and their IP have experienced as a result of the substance use and the nature and outcome of previous attempts to change the IP's behavior. Overall, these discussions lay the foundation for motivating CSOs to work hard in treatment with a totally new strategy.

Clinicians establish positive expectancies by outlining the research support behind CRAFT, namely, that CRAFT is highly effective in helping IPs engage in treatment (nearly 7 out of 10 times) and in decreasing the distress experienced by the CSO regardless of whether the IP enters treatment. Furthermore, clinicians emphasize that CRAFT is effective across a wide variety of CSO-IP relationships (e.g., spouse, friend, parent), ethnicities, and substances. The clinician then outlines the basic premises involved in CRAFT and the three main goals: (1) decrease the IP's substance use, (2) get the IP to enter treatment, and (3) increase the CSO's happiness independent of the IP's decision to enter treatment.

57.2.4.2 Functional Analysis of IP's Substance-Using Behavior

Similar to the functional analysis (F.A.) that is completed with the substance-using individual during CRA, an F.A. also is completed as part of CRAFT, but with the *CSO* providing the information about the IP. First, the triggers that usually precipitate the IP's substance use are outlined, and then the positive and negative consequences of the use are delineated. The CSO's challenge is to influence/change the IP's environment so that the IP responds in a healthier manner to triggers but in a way that still allows the IP to experience some of the positive consequences (and none of the negative consequences) that have been associated with the substance use. For example, if it is determined that the IP typically views 5 PM as the time to meet with friends to alleviate stress after work (and this typically occurs at a bar), the CSO could help arrange some nondrinking social activities with friends for 5 PM.

Alternatively, the CSO could urge the IP to come straight home after work so that the two of them could go for a relaxing walk in the park. Ideally the exercise and the conversation would serve as a suitable substitute for the "unwinding" in the bar. By choosing a substance-free activity, the IP will not only experience positive consequences but will also experience a reduction in the negative consequences that typically follow substance use. Using a gentle approach, the CSO can help the IP recognize that the negative consequences of substance use (e.g., trouble getting up for work the next day) are eliminated when the IP engages in the substance-free alternative.

It is important to realize that simply making one change in behavior will not suddenly solve the IP's substance use problem. Instead, the CSO typically needs to introduce a number of changes (as outlined in the remaining CRAFT procedures below) before the IP decides to seek treatment.

57.2.4.3 Domestic Violence Precautions

As part of CRAFT, CSOs are taught to modify their own behavior such that only substance-free IP behaviors are "rewarded." Furthermore, CSOs learn to allow IPs to experience the natural negative consequences of substance use. Domestic violence precautions are an important topic to consider before the CSO considers modifying any behavior at home, given that IPs routinely are not pleased with these CSO behavior changes *and* a high correlation already exists between domestic violence and substance use (Klostermann et al. 2010). Thus, CRAFT clinicians always assess the risk for domestic violence, and in some cases CSOs are referred to other programs. At times, functional analyses are used to outline the common triggers for an IP's aggressive behavior, and plans for keeping the CSO safe are stressed. Regardless, CRAFT clinicians regularly ask CSOs to anticipate their IP's probable reaction to a specific change in the CSO's behavior that is under discussion as a potential homework assignment.

57.2.4.4 Communication Skills

Effective communication skills are essential for several CRAFT procedures, including the ultimate invitation for the IP to enter treatment. In the earlier stages of treatment, CSOs' reliance upon positive communication skills can help minimize IP defensiveness and anger when explaining the rationale behind the CSO's own behavior change and when specifically requesting changes in the IP's behavior. The basic components of positive communication for CRAFT are the same as those introduced for CRA: offer an understanding statement, accept partial responsibility, and offer to help. Assume that a mother (CSO) is trying to get her 22-year-old son (IP), who recently received a DUI, to spend time at an alcohol-free music establishment with a nondrinking friend on a Friday night. The CSO might be encouraged to say, "Honey, I know you'd really prefer to be with your old buddies tonight (*understanding statement*), and maybe I shouldn't have meddled by checking to see if Kenny was available (*partial responsibility statement*). But I know you and Kenny still like to get together occasionally, and you both love music. And this place in town has gotten great reviews. Will you give it a try? I'll even arrange your

transportation if you want (*offer to help*)." As noted previously, communication skills are taught through repeated practice in the context of role plays.

57.2.4.5 Positive Reinforcement for Clean and Sober IP Behavior

It is important for CSOs to fully realize that individuals are more likely to repeat behaviors that are reinforced (rewarded), and thus, when CSOs actively reward sober behaviors, they are increasing the likelihood that those sober behaviors will be repeated. CSOs also must understand the distinction between CRAFT's positive reinforcement (which increases the likelihood of clean/sober behaviors) and "enabling," which inadvertently increases the likelihood of substance use. Once the concept of positive reinforcement is explained, clinicians work with CSOs to develop a plan for administering reasonable rewards for the most appropriate times and occasions. The reward always should be inexpensive and readily available, but the type of reward varies based on the CSO-IP relationship, the personal preferences of the IP (i.e., what the IP really enjoys), and what the CSO feels comfortable offering. Some common examples include CSOs giving a compliment, cooking a favorite food, giving a hug, spending pleasant time with the IP, or doing a favor. Since it is imperative that the rewards follow sober behavior, CSOs sometimes require training in discerning whether or not the IP has engaged in substance use recently. If CSOs are interested in explaining the rationale for the reward to their IP, positive communication skills (noted above) are rehearsed. For example, a CSO might say to the IP, "I know it's important to you that I spend some time with you after dinner (*understanding statement*), and I haven't been doing a great job of that lately (*partial responsibility*). So I'm willing to sit and watch TV with you tonight (*offer to help*), but only if you don't get high. You're a lot of fun to be with when you're not using." The importance of the CSO leaving the situation (but without any argument or "drama") if the IP ended up smoking would be stressed.

57.2.4.6 Negative Consequences for Substance-Using Behavior

Just as a behavior is likely to be repeated if it is rewarded, a behavior is *less* likely to be repeated if it is followed by a *decrease* in rewards or an *increase* in negative consequences. CSOs can play an active role in reducing the IP's substance use by withdrawing the same rewards mentioned above (or additional ones) when the IP has been using substances. CSOs typically feel more comfortable removing rewards if they have discussed the rationale for needing to do so with the IP well in advance. Again, positive communication is essential, and the risk for a violent IP reaction is discussed.

CSOs tend to care greatly about the well-being of their IP and consequently find themselves engaging in certain behaviors over time that unintentionally interfere with the natural, negative consequences of their IP's substance use. For example, by helping the IP into bed after a night of drinking, the CSO is preventing the IP from experiencing the full natural (negative) consequences of the decision to use substances. Clinicians discuss the potential ramifications of CSOs changing their own behavior (i.e., *not* helping the IP into bed), including whether it would create more problems than it would solve. For example, an IP might lose a job and thus

financially damage the entire family if the CSO did not call in sick for a hungover IP. But if deemed an appropriate behavior to target, a specific plan for changing the CSO's behavior would be developed. If the CSO wanted to explain the plan to the IP, the conversation would be rehearsed.

57.2.4.7 Helping CSOs Improve Their Own Lives

Unfortunately it is the norm for CSOs to present with a great deal of distress, often in the form of anxiety, depression, or physical symptoms (Orford et al. 1998). A primary goal of CRAFT is to help CSOs improve their own lives, regardless of whether the IP decides to enter treatment. CSOs complete the Happiness Scale (from the CRA protocol) so that their degree of satisfaction across ten personal life domains can be assessed and goals can be set. For example, assume a CSO has become isolated socially and thus rates "social life" a "3." The CSO and clinician might work together to create a plan to broaden the CSO's social network by getting the CSO involved in a new recreational activity or reaching out to an old friend. As always, potential obstacles would be anticipated and addressed, including a possible negative reaction from the IP.

57.2.4.8 Inviting the IP to Sample Treatment

Although CSOs are eager to invite their IP to enter treatment, CRAFT clinicians caution them to lay a solid foundation first. This includes spending some time employing the various CRAFT procedures just outlined, such as rewarding nonusing IP behavior, introducing negative consequences for IP substance use, and relying on positive communication skills throughout. Perhaps not surprisingly, CSOs often report that their IP's substance use has decreased somewhat prior to the IP agreeing to seek treatment. In addition to allowing time for the CRAFT procedures to have an effect, CSOs need to learn the communication skills required for extending the invitation and to identify the ideal time to have the conversation with the IP. Regarding the latter, CSOs are taught to extend the invitation at a time when the IP is most likely to be willing to sample treatment. These "windows of opportunity" may occur when the IP is remorseful about a substance-related negative consequence, upset about a remark about his/her substance use, curious about what the *CSO* is addressing in treatment, and questioning why the CSO's behavior has changed.

"Motivational hooks" are incorporated into the treatment invitation, such as pointing out that IPs can have their own therapist (separate from the CSO's clinician), highlighting that therapy can help the IP in non-substance use domains as well (e.g., finding a job, decreasing anxiety or depression), and suggesting that the IP sample a session or two without making a full commitment to therapy. CSOs should be taught that if their IP initially declines the invitation, they should continue engaging in their new CRAFT-consistent behaviors in order to increase the likelihood of treatment engagement in the near future. Importantly, clinicians need to do preparatory work to ensure that a therapist is available to see the IP without delay as soon as the IP agrees to sample treatment. Furthermore, the IP's therapist should have a theoretical approach consistent with CRAFT, such as a behavioral or cognitive behavioral orientation.

57.2.5 CRAFT Scientific Support

Prior to the development of CRAFT, a few traditional programs were available for the loved ones of treatment-refusing individuals with substance use problems: Al-Anon/Nar-Anon and the Johnson Institute Intervention. Al-Anon (Al-Anon Family Groups 1984) was shown to provide good emotional support (Barber and Gilbertson 1996; Dittrich and Trapold 1984), but many CSOs were uncomfortable with the message to "detach" from their IPs. The Johnson Institute Intervention (JII; Johnson 1986), in contrast, was specifically geared toward working through CSOs in order to get a resistant individual into treatment. After several planning sessions with multiple CSOs, a "surprise party" was scheduled in which the CSOs confronted the IP with the substance use problem and its ramifications. Studies showed that when families actually carried out the entire intervention, the treatment engagement rate was high, but the vast majority of people dropped out of the program before the final meeting with the IP (Liepman et al. 1989), potentially due to concerns over the effect of the intervention on the relationship with the IP (Barber and Gilbertson 1997).

Unilateral Family Therapy (UFT) was introduced in the early 1980s as a type of family therapy that involved individuals other than the IP. Thomas and colleagues conducted several studies with UFT and found promising results, but the studies tended to be small and lacked good experimental controls (e.g., Thomas and Ager 1993; Thomas et al. 1987). Another UFT program with some scientific support was Pressures to Change (e.g., Barber and Crisp 1994; Barber and Gilbertson 1997). Finally, ARISE (A Relational Intervention Sequence for Engagement) is an "invitational" intervention that uses different levels of treatment (e.g., starting with phone conversations with CSOs) and informs the IP about the ongoing meetings with CSOs throughout. Much of the evidence to date has been promising case reports and a pilot study (see Landau and Garrett 2008).

CRAFT, a type of UFT, originally was called CRT (Community Reinforcement Training) when the first small study was conducted by Sisson and Azrin (1986). Twelve female CSOs were randomly assigned into either CRT ($n = 7$) or individual counseling + Al-Anon referrals ($n = 5$). Six of the seven women in the CRT group (86 %) were able to get their problem-drinking IPs into treatment compared to none of the IPs in the comparison group. The second CRAFT study that focused on IPs with alcohol problems was a large NIAAA-funded project that randomly assigned 130 CSOs into one of the three treatment groups: CRAFT, Al-Anon Facilitation Therapy (an individual therapy version of Al-Anon; Nowinski et al. 1992), or the Johnson Institute Intervention. Results indicated that CRAFT-trained CSOs were significantly more effective in engaging unmotivated problem drinkers in treatment (64 %) as compared with the CSOs in the more commonly practiced Al-Anon (13 %) and Johnson interventions (30 %; Miller et al. 1999). Interestingly, CSOs improved in their own functioning independent of treatment condition and whether their IP entered treatment. For those IPs who entered treatment, they did so with their CSOs receiving an average of only 4.7 CRAFT or Al-Anon sessions and 5.7 Johnson Institute sessions.

The success of CRAFT also has been established for treatment-refusing IPs with illicit drug problems. In a pilot project, 62 CSOs from diverse ethnic backgrounds were trained in the CRAFT protocol. As expected, the CSOs were able to get a high percentage of IPs (74 %) into treatment very quickly (less than five CSO sessions) while also reducing the CSOs' own levels of depression, anxiety, and anger (Meyers et al. 1999). At about the same time, a CRAFT (CRT) study was conducted by Kirby and colleagues in which 32 CSOs were randomly assigned to either CRT or 12-step meetings. Engagement rates were 64 % for the CRT-trained CSOs and 17 % for CSOs in the 12-step condition (Kirby et al. 1999).

A large NIDA-funded study was conducted next in which 90 CSOs of illicit drug using IPs were randomly assigned to CRAFT, CRAFT + Aftercare, or Al-Anon/Nar-Anon Facilitation Therapy. An aftercare component was added to one of the CRAFT conditions to mimic the availability of ongoing aftercare groups within the 12-step model. The results demonstrated that the combined CRAFT conditions' engagement rates (67 %) were significantly higher than the Al-Anon/Nar-Anon rates (29 %), but there were no significant engagement differences between the two CRAFT conditions (Meyers et al. 2002). More recently an effectiveness study demonstrated that CRAFT could be successfully transferred from a controlled research setting to a community treatment agency, while maintaining levels of engagement quite similar to previous controlled studies (Dutcher et al. 2009).

CRAFT's success with adults was tested with adolescents in an uncontrolled trial that recruited the parents of 42 drug-abusing, treatment-refusing adolescents (Waldron et al. 2007). A total of 71 % of the parents engaged their adolescents into treatment using CRAFT, and the parents overall experienced a significant reduction in negative symptoms. Another unique application of the CRAFT protocol was a study that delivered CRAFT in a group treatment format (Manuel et al. 2012). Participants were randomly assigned to a CRAFT group or to self-directed CRAFT, with the latter receiving the CRAFT self-help book (Meyers and Wolfe 2004). The intent-to-treat analysis contrasted the CRAFT group engagement rate (60 %) with the self-directed CRAFT rate (40 %) and detected no statistically significant difference. However, for those CSOs assigned to the CRAFT group condition who attended at least one session, 71 % engaged their IP into treatment. The implication is that group CRAFT can be a cost-effective method of getting treatment-refusing IPs into treatment.

CRAFT has been found superior in engaging treatment-refusing substance-abusing individuals compared with traditional programs. Additionally, CRAFT has been shown effective across ethnicities, different types of CSO-IP relationships, and various kinds of drugs of abuse. Furthermore, CRAFT works in less than five CSO sessions on average, and CSOs report psychological improvement regardless of the outcome of their engagement efforts.

57.2.6 International Considerations

The CRAFT training manual, *Motivating Substance Abusers to Enter Treatment: Working with Family Members* (Smith and Meyers 2004), has been translated into

German, Korean, Finnish, and Japanese to date. The self-help version (Meyers and Wolfe 2004) is available in Finnish and Spanish. Therapists have been trained in CRAFT across the world, including Ireland, Wales, Scotland, the Netherlands, Sweden, Finland, Germany, and Canada.

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Development and Dissemination of the Matrix Model of Intensive Outpatient Treatment

58

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Contents

Abstract

The Matrix Model of intensive outpatient treatment was developed in the 1980s to address the needs of stimulant users. Over time, a manualized treatment protocol was developed and published, and the application of the Matrix Model was extended to other drug and alcohol users. A randomized, controlled, multisite trial was funded by the Center for Substance Abuse Treatment to evaluate the Matrix Model compared to "treatment as usual" with 978 methamphetamine users at eight sites. The results of this study were the basis for the Matrix Model achieving the designation as an evidence-based program. In the late 1990s, the methamphetamine epidemic combined with the funding

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requirement that providers use evidence-based treatments resulted in a high demand for training programs in the use of the model. Matrix developed standard training curricula, fidelity instruments, and quality assurance protocols. Training procedures consist of an initial 2-day, core training session followed by more intensive training with the person at each site identified as the "Key Supervisor." Sites are certified after passing a site visit and review of audiotaped sessions. In addition to the dissemination of the Matrix Model across the United States, training has been delivered in 21 countries worldwide with certified programs in South Africa, Nicaragua, Guam, Spain, New Zealand and Abu Dhabi.

58.1 Introduction

58.1.1 Matrix Model Background

The Matrix Model of outpatient treatment was developed at the height of the stimulant epidemic in Southern California in the 1980s (Obert et al. 2000). In the urban areas of Los Angeles, crack cocaine was the major drug problem affecting communities, but 50 miles to the east of downtown Los Angeles, in San Bernardino County, large numbers of methamphetamine (MA) users began to present at the Matrix Institute on Addiction clinic in Rancho Cucamonga (one of three Matrix clinics in the Southern California area) for assistance. At the time, there was no established approach for structuring outpatient services to meet the needs of these two groups of stimulant users. Therefore, with funding from the National Institute on Drug Abuse (NIDA), the authors of the Matrix approach attempted to integrate existing knowledge and empirically supported techniques into a single, multielement manual that could serve as an outpatient "protocol" for the treatment of cocaine and MA users (Rawson et al. 1989, 1995).

The development of the Matrix Model was influenced by an ongoing interaction between clinicians working with patients and researchers collecting clinical research data. As clinical experience with stimulant-dependent individuals was amassed, clinical impressions frequently generated questions that were answered by using relevant research findings. For example, stimulant users in outpatient treatment frequently gave the impression of being unmotivated or uncooperative because they failed to comply with counselors' directions. At the time (mid-1980s), many treatment programs considered these patients to be "in denial" and often confronted them aggressively or discharged them as "not ready for treatment." New information on stimulants and the brain provided an alternate view of these patients for Matrix clinicians. They began to understand that it was not "denial and resistance" but rather a neurobiological issue involving brain chemistry changes that contributed to patients' inability to recognize and deal rationally with their self-destructive behavior.

As Matrix staff worked with these stimulant users, they identified specific clinical issues (e.g., conditioned cues, drug craving, anhedonia) that created challenges for patients. Materials were adopted from the cognitive behavioral and

relapse prevention literature to provide patients with an understanding of these phenomena and with "tools" to deal with them. Matrix staff also identified a set of clinical issues in working with the family members of these patients, and therefore, materials were adapted from the family therapy literature to aid in working with family members. In order to standardize the delivery of a common set of materials across patients, therapists, and clinics, a treatment manual was created that consisted of a session-by-session set of clinical exercises and information (Rawson et al. 1989, 1995). At the Matrix clinics, as in most treatment settings, the patients presented using alcohol and other drugs as well as stimulants. Even those patients who were non-stimulant users found the approach relevant and had a treatment response that was similar to that of the stimulant users.

The initial manual for the Matrix Model of intensive outpatient treatment was produced with funds from NIDA (Rawson et al. 1989) and evaluated in a major multisite trial (see below) by the Substance Abuse and Mental Health Services Administration (SAMHSA; Rawson et al. 2004). The Matrix manual and supportive materials are available at www.ncadi.samhsa.gov. Subsequently, Matrix Model manuals that are not specific to stimulants, that have more family and individual sessions, and that include a section on Medication Assisted Treatment as well as versions that are specifically geared for use with adolescents and with drug courts were published and are available from Hazelden Publishing at www.hazelden.com. Research reports describing clinical experiences with the model, on the application of the entire package of techniques (Rawson et al. 1995, 2004; Huber et al. 1997).

58.2 Elements of the Matrix Model

58.2.1 Description

The 16-week Matrix intensive outpatient treatment protocol is delivered in meetings that occur three times each week. A primary therapist conducts both the individual and group sessions for a specific patient and is responsible for coordinating that patient's entire treatment experience.

58.2.1.1 Program Components

- **Early Recovery Groups** occur biweekly for 4 weeks at the beginning of treatment. The content of these groups is designed to teach basic skills and provide information to help patients stop using drugs and alcohol.
- **Relapse Prevention Groups** are the critical mechanism for supporting recovery and helping patients learn how to maintain abstinence. These groups are delivered biweekly over the entire 16-week treatment period. The content of the materials used in these groups emphasizes cognitive behavioral therapy concepts and skills. Matrix group leaders coach patients through the recovery process. The groups are quite directive and maintain a focus on the topic materials; they are not used as process or psychotherapy groups.

- **Family Education Groups** are designed to explain addiction in simple terms. These groups cover the biology of addiction (e.g., neurotransmitters, brain structure, drug tolerance), principles of learning and conditioning as they apply to addiction, the medical effects of drugs and alcohol on organ systems, and how addiction impacts family relationships. Because Matrix trainers are experienced in working with various cultures within and outside of the United States, important culturally specific materials are included within the Education Group curriculum. Several of the lectures are essential to the understanding of the skills taught in all components of the Matrix program. One of the lectures covers the changes in brain chemistry as the brain recovers from the neurochemical changes produced by drug use (Roadmap for Recovery). Another lecture presents information derived from research about the role of classical conditioning in the development of drug craving and why craving is stimulated by specific cues and emotional states (Triggers and Cravings). The lectures have been produced in DVD format by both the Center for Substance Abuse Treatment (CSAT) and Hazelden.
- **Individual Sessions** provide the therapists and patients with a setting to individualize the treatment experience and address issues that may be too personal to cover in group sessions. Frequently, individual sessions include significant others and/or family members, which allows relationship issues to be addressed. The frequency of individual sessions is geared to the patient's needs and can be adjusted to address crisis situations.
- **Urine/Breath Tests** are conducted randomly on a weekly basis, and the results are used to review and improve the treatment plan, not to police or punish.
- **Social Support Groups** are provided beginning at week 13 of treatment and continue as part of an ongoing continuing-care program. In these groups, patients are able to interact with drug-free friends and are encouraged to engage in new recreational behaviors that promote a drug-free lifestyle.
- **12-Step Meetings** are an adjunct to the Matrix Model and are optimally held on-site one night a week to introduce patients to AA concepts and philosophy. Patients are strongly encouraged to participate in community 12-step groups and use the 12-step program as a long-term source of support.

58.2.1.2 A Positive and Collaborative Therapeutic Relationship

The Matrix Model is characterized by a positive and collaborative relationship between the patient and therapist. Within this model, the therapist is directive but maintains a patient-centered therapeutic stance. The motivational interviewing (MI) techniques developed by Miller and Rollnick (1991) are used to create the positive and motivating therapeutic relationship necessary to deliver the Matrix treatment approach. This caring relationship, described by Rodgers as containing empathy, positive regard, warmth, and genuineness (Rogers 1951), is the basis for both MI and the Matrix Model. A collaborative therapeutic climate that communicates acceptance without judgment and that moves at the patient's pace increases patients' readiness to learn new skills, provides practice for more adaptive coping strategies, and facilitates change.

58.2.1.3 Structure and Expectations

The schedule of the Matrix program provides a structure that gives patients thrice weekly clinic visits across the initial 16 weeks of treatment. Between visits to the clinic, patients are assisted in developing a structure and schedule that helps build routines consisting of low-risk activities and situations. The primary tool in building a structure is creating a daily, hour-by-hour schedule for their activities. Proactively planning future activities and following through on this plan is frequently a new skill for many patients. Mastering this skill of purposely determining behaviors, as opposed to acting with no plan, is an important step toward creating a drug-free lifestyle. Creating a written schedule with patients can help them operationalize how to stay abstinent "one day at a time."

58.2.1.4 Psychoeducation

The Matrix Model includes educating patients about conditioning and neurobiology to help them understand the concept of addiction as a "brain disease" (Obert et al. 2002). The educational materials used in the Matrix program help patients recognize the physiology/neurobiology of addiction and remove some of the confusion they have about their own feelings, thinking, and behavior. This knowledge is used to empower patients to take steps to actively become change agents in building a recovery program. While the Family Education component of the program is a major forum for presentation of psychoeducational materials, an educational aspect of the Matrix program is included in all treatment activities.

58.2.1.5 Teaching Cognitive Behavioral Skills

Knowledge and skills developed as cognitive behavioral therapy exercises (CBT) play a large role in the Matrix Model. The work of Marlatt and Gordon (1985), Carroll and colleagues (1991, 1994a, b), and others has contributed greatly to the content and group treatment activities of the Matrix Model. While this form of cognitive behavioral outpatient therapy is structured and focused on relapse prevention, it has been customized across cultures and continents to address patients' unique experiences, thoughts, and behaviors. The educational aspect of CBT teaches patients how to self-monitor and avoid relapse as they interact with the cues and high-risk situations they encounter. In the group format used in the Matrix Model, patients are asked to report on strategies that worked and those that did not work, what obstacles were encountered, and what changes need to be made to make the interventions successful in the future. Each of the Matrix group sessions is anchored by a specific topic. Patients leave each group with information and skills about recovery and how it applies to their situation. The therapist in these groups combines teaching skills with motivational interviewing strategies to help facilitate the use of the recommended strategies. The Matrix program has sometimes been described as an experience more closely related to taking a course in recovery knowledge and skills than a process of psychotherapy.

58.2.1.6 Positive Reinforcement

Research and empirical evidence supports the use of contingency management (CM) techniques to shape and maintain drug recovery behaviors (Petry 2000; Roll et al. 2006). These techniques are, at their core, the systematic application of positive reinforcement principles to the modification of behavior. As the research evidence has accumulated on the effectiveness of CM (Rawson et al. 2006; Roll et al. 2006), CM strategies have been added as a standard component of the current Matrix Model treatment. Positive reinforcement to promote behavior change can be accomplished in ways other than with CM. One technique for reinforcing positive behavior is the recording of sober days on a calendar. To implement this exercise, patients are asked at the beginning of each session to place colored stickers, or "dots," on a calendar for each drug-free day. This public recording of abstinent days provides an excellent opportunity to explicitly reinforce patients' achievements.

58.2.1.7 Family Involvement

The Matrix Model involves family members in the treatment program in both the individual sessions and the Education Groups. "Family" includes all those people who are part of patients' everyday life. These individuals include biological family members as well as partners, close friends, associates, and extended family members. Family involvement in the Matrix Model leads to better retention of patients in the treatment. It is not uncommon for some patients to not want family members involved, especially those family members who are critical or overly controlling. It is often helpful for therapists to schedule a session with family members to explain the ways in which they can be involved in the treatment process and to encourage them to attend scheduled sessions. Family members are often willing to help support the recovery process and attend treatment when their role is presented as providing supportive and positive assistance, as opposed to asking them to enter "therapy" for their family systems pathology. While getting families to participate is sometimes difficult, it is often possible to find at least one family member who is willing to be a part of the treatment process. Matrix therapists proactively reach out to family members to promote their active involvement in the scheduled treatment activities.

58.2.1.8 Self-help Groups

Research has demonstrated the usefulness of participation in 12-step programs in achieving and maintaining recovery from addiction (e.g., Humphreys et al. (2004)). Attending 12-step meetings is strongly encouraged as part of the Matrix treatment experience. In countries where the 12-step program is not available or is inconsistent with the culture, other types of fellowships and sober social activities can be added to the program. Often, motivational interviewing strategies can be helpful in encouraging involvement in 12-step meetings.

58.2.1.9 Urine and Breath Tests

The Matrix approach requires accurate information on the drug use of patients as they progress through treatment. The most accurate means of monitoring patients

for drug and alcohol use during treatment is through the use of urine and breath alcohol testing. Urine testing is used as a way to reveal continuing drug use, which is a sign that the treatment plan needs revising. Urine and breath alcohol testings done in a clinical setting for clinical purposes are quite different from urine testing that is done for legal monitoring.

58.2.2 Matrix Model Randomized Clinical Trial

The Matrix Model was evaluated in a randomized, controlled study funded by CSAT with 978 methamphetamine users in a national multisite trial (Rawson et al. 2004). The design involved a comparison of the Matrix approach with eight different forms of treatment as usual (TAU). This was not an optimal efficacy design, but it was necessitated by CSAT's desire to provide as much treatment as possible within an evaluation study. The eight sites differed considerably: one site provided treatment in the context of a drug court, another site treated women exclusively, and two sites treated a significant number of Asians and Pacific Islanders. The remaining sites provided care primarily to Caucasian and Hispanic participants. All sites employed outpatient treatment models, but the elements of TAU varied widely at each treatment site.

The participants in the study had on average 7.54 years of lifetime MA use and 11.53 days of MA use in the past 30 days. The preferred route of administration of MA was smoking (65 %), followed by injecting (24 %) and snorting (11 %).

During the application of the Matrix Model, the participant performance in seven of the eight sites was clearly superior in the Matrix condition, compared to the TAU condition (the lone exception was within the drug court, a mandated program, where there was no difference between conditions). Matrix Model treatment resulted in participants attending more sessions, staying in treatment longer, providing more methamphetamine-free urine samples, and having longer periods of methamphetamine abstinence. Compared to those who participated in TAU, 38 % of Matrix clients were more likely to stay in treatment, 27 % were more likely to complete treatment, and 31 % were more likely to have methamphetamine-negative urine test results. However, outcomes at discharge and follow-up were comparable between patients treated in the Matrix Model and those treated with TAU.

Overall, across the study, MA use decreased substantially during treatment. At enrollment, participants reported approximately 11 days of use in the last 30 days, whereas at discharge, the number was reduced to approximately 4 days of use in the last 30 days. At the 6-month follow-up, the number was still approximately 4 days and it decreased even more at the 12-month follow-up (approximately 3 days). This reduction in drug use from enrollment to the 6- and 12-month follow-up points was consistent across sites and conditions. The results of this study were the primary basis for the Matrix Model achieving inclusion in the SAMHSA's National Registry of Evidence-based Programs and Practices.

58.2.3 Dissemination of the Matrix Model

Matrix Model training efforts, both within the United States and internationally, began in the late 1990s, as many areas in the United States and other regions sought direction on approaches for the treatment of amphetamine-type stimulant (ATS) use disorders. In order to accommodate these training requests, a model for dissemination of the Matrix Model was developed that would not be too restrictive (both in terms of cost and fidelity requirements) but would create local expertise to provide ongoing training and supervision of clinical staff and ensure fidelity to the main components of the model. Consultation on the development of a dissemination model was obtained from Texas Christian University, the University of South Florida, and the National Implementation Research Network. The Matrix Model training process ideally begins with a pre-training phone consultation with the organization where staff are to be trained, in order to review the setting, staff, and population to be treated and explain the overall training plan. The first training component is a two-day training on the Matrix Model that is attended by the organizations' clinical and administrative personnel. The organization leadership, with input from Matrix trainers, selects the trainee clinicians to be developed as local Matrix experts. These local experts are referred to as Matrix Key Supervisors. Key Supervisors should be:

- Respected clinical leaders who are both credible to clinicians and knowledgeable about organizational dynamics
- People who possess excellent communication and clinical skills
- Leaders who are committed to actively working to implement the Matrix Model with fidelity and good effect

After attending the core training, Key Supervisors are trained in a two-day training that includes instructions on how to teach the model and monitor fidelity to it, how to supervise clinical staff in delivering the model, and how to train new clinical staff who join the program after the initial training.

58.2.3.1 Matrix Trainers

The trainers who lead the Matrix Model dissemination efforts are skilled teachers with extensive experience training mental health professionals, and they have extensive experience delivering and supervising Matrix treatment. In addition to being knowledgeable about the Matrix materials, Matrix trainers are skilled in helping problem-solve implementation issues, addressing clinician and organizational resistance to change (employing their motivational interviewing skills), and creating a training experience that is a mix of didactic and role-play activities.

58.2.3.2 Certification

The Matrix Institute developed a certification program in response to requests by state agencies for a way to determine which programs were delivering the Matrix Model with adequate training and fidelity to the model. The Matrix certification confirms that the organization has been delivering the model for at least 6 months, has clinicians who are properly trained, and has Key Supervisors who oversee the implementation and supervise the clinical staff.

58.2.3.3 Dissemination Activities

The Matrix Model has been extensively disseminated in the United States. A major impetus for people and agencies to receive this training is that during the past decade, there has been a major push by SAMHSA and professional groups to promote the use of evidence-based practices (EBP). With the designation of the Matrix Model as an EBP via the SAMHSA NREPP program, the Matrix Model represents one of the few EBPs for treating individuals with drug dependence. Matrix dissemination efforts in the United States and internationally have led to over 6,000 individuals and 320 Key Supervisors being trained by Matrix trainers. Matrix trainers have conducted training sessions in 21 countries, in all 50 states, and have trained staff from 2,500 treatment agencies. Fourteen agencies in the United States have received Matrix certification, as have ten international agencies (in South Africa, Spain, Abu Dhabi, Guam, New Zealand, and Nicaragua). The Matrix manuals have been translated into many languages including; Thai, Arabic, Farsi, Spanish, Portuguese, Vietnamese, Slovakian, Afrikaans, and Japanese.

58.2.3.4 International Dissemination Efforts: Examples

In many parts of the world, the use and abuse of ATS are major public health problems, and therefore, effective treatments are in great demand. At present, there are no pharmacotherapies with demonstrated efficacy for ATS use disorders. Demand for training in the Matrix Model appears to be the result of clinical leaders in many parts of the world searching for an integrated package of treatment techniques for ATS disorder treatment that can be systematically implemented and evaluated.

58.2.3.5 South Africa

The first Matrix Model training in South Africa was in 2006, hosted by Substance Misuse: Advocacy, Research, Training (SMART), a nonprofit organization. SMART has hosted five trainings in the Western Cape in 2006, 2008, 2011 (two visits), and 2012. An additional training was hosted by the Bosasa Youth Development Centers in Gauteng, South Africa. Each of these training sessions included at least one core and a Key Supervisor Training, with participants from national, provincial, and city agencies and private treatment centers. Five of the Matrix sites are located in city and provincial community health centers in Cape Town and the Western Cape. While there are many Matrix programs in South Africa, fourteen are presently certified with ten of these within Bosasa. These programs report excellent results with very diverse populations, and it is expected that additional sites will be certified in the future.

58.2.3.6 Spain

The first Matrix Model training in Spain was sponsored by the government of Murcia in 2005. Three major training events have been conducted in the region of Murcia, in which more than 80 professionals and four Key Supervisors have been trained. Despite severe economic obstacles, efforts are underway to ensure continuity of implementation, training, monitoring, and evaluation efforts with the Matrix Model throughout Spain.

58.2.3.7 Abu Dhabi

The National Rehabilitation Center (NRC) in Abu Dhabi, United Arab Emirates, is a regionally significant treatment center in the Gulf region that has been operating since 2002. As increased demand for services was recognized, the NRC began a major expansion of services in 2010. One area of need that was identified was the establishment of a program of outpatient services. In 2011, the NRC hired a psychiatrist trained for 2 years at the Matrix Institute and UCLA. He began implementation of the Matrix approach in a limited manner, and after a 1-year pilot test period, the NRC leadership initiated a plan to fully implement the Matrix program and complete the certification process. Trainings have been conducted in the Matrix Model in Abu Dhabi, and in 2012, a team for four Emirati clinicians (one MD and three psychologists) visited the Matrix offices in Los Angeles for 6 weeks for an intensive training experience in the Matrix Model. At present, they are completing the certification process. One result of the Matrix training has been a very significant expansion of outpatient services at the NRC, as the number of patients in outpatient treatment has increased and the Matrix program has promoted the organization and delivery of a diverse set of services for patients.

58.3 Conclusion

The Matrix Model is a treatment approach comprising a collection of evidence-based strategies, integrated into a single protocol. The research on the Matrix approach (Rawson et al. 1995, 2004; Huber et al. 1997) supports its value as a standardized package, but the treatment elements have been disaggregated into individual elements and applied in a variety of treatment settings in countries and areas including Japan, Vietnam, Egypt, Palestine, Israel, Australia, the Caribbean, Guam, China, Brazil, and Canada. The primary attraction of the Matrix approach is that it has research evidence to support its effectiveness, it uses evidence-based treatment elements, and it has been manualized. Further, in many international sites, the development of outpatient services is in the early phases, and the Matrix Model provides a way of organizing services within a structured framework.

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Exercise for Substance Use Disorders

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Abstract

This chapter provides an overview of the rationale and evidence for exercise as a treatment intervention for substance use disorders. The benefits of exercise on physical health, including weight and cardiovascular outcomes, are well known; emerging literature also supports the use of exercise in reducing depression and anxiety symptoms. These and other negative affect states are common during withdrawal and early abstinence from substances and may predispose users to relapse. Exercise may facilitate abstinence by enhancing positive mood states via effects on the endogenous opioid system and potentiation of dopaminergic transmission. Furthermore, cognitive deficits have been observed in long-term substance users, and exercise has been associated with improvement in cognitive functioning, particularly executive control tasks. The addition of a new, non-drug-related activity such as exercise may provide a reinforcing alternative behavior that may complement relapse prevention skills taught in common therapy approaches for substance users while promoting health and positive behavioral changes consistent with treatment goals.

59.1 Introduction

There is clear scientific evidence that physical exercise can have a positive effect as an intervention for a variety of medical and psychiatric disorders and symptoms. As noted in the *2008 Physical Activity Guidelines for Americans* (Leavitt 2008) and elsewhere (e.g., Lautenschlager et al. 2008; Palmer et al. 1995), exercise appears to have generally beneficial effects on mood, cognition, and health. In addition, exercise has been shown to have positive effects in mediating many of the conditions that are associated with substance use. Research has shown that individuals addicted to drugs and alcohol experience high levels of negative affect states including depression and anxiety, which may be ameliorated by exercise (e.g., Reed and Ones 2006). Cognitive impairment (Kramer and Erickson 2007), fatigue, and low energy (e.g., Häuser et al. 2010) associated with drug use may also improve as a result of exercise.

Direct experience in treating stimulant users has demonstrated the benefits of exercise. For example, clinicians at the Matrix network of addiction treatment clinics in Southern California observed that anhedonia and cognitive disruption that persisted for months after cessation of use appeared to be significantly less severe among those individuals who engaged in regular exercise as part of their recovery plan (Rawson et al. 2002). This observation became the basis for a recommendation appearing in a clinical guide publication: “the experience at Matrix over the past 20 years has

suggested that if patients can be engaged in a program of physical exercise, they are more able to manage difficult emotional states. An exercise program, three to five times per week, appears to help relieve symptoms" (Rawson 2006). This chapter recounts the experience of the author and colleagues who have employed exercise in a clinical research study conducted in a community-based residential treatment program serving patients with stimulant use disorders; initial discussion provides a brief rationale for exercise as an intervention for substance use disorders.

59.2 Exercise as an Intervention for Health Conditions Associated with Substance Use Disorders

59.2.1 Exercise Is Effective for Medical Conditions and Symptoms

Based on a comprehensive review of the literature, the US Department of Health and Human Services presented the *2008 Physical Activity Guidelines for Americans* (Leavitt 2008), documenting "strong evidence" for general health benefits of physical activity. For adults, improvements ensuing from regular exercise at moderate levels were lower risk of early death, heart disease, stroke, diabetes, high blood pressure, adverse blood lipid profile, metabolic syndrome, and colon and breast cancers. Exercise is helpful for prevention of weight gain, weight loss when combined with diet, and improved cardiorespiratory and muscular fitness, as well as reduced depression and better cognitive function.

Exercise has been shown to reduce fatigue in individuals with multiple medical conditions, including fibromyalgia (Häuser et al. 2010) and ankylosing spondylitis (Durmus et al. 2009). The benefits of exercise in reducing chronic pain have also been extensively documented in prior literature (Hayden et al. 2005), including reductions in lower back pain and functional outcomes from prescribed aerobic (McDonough et al. 2010) and resistance (Shirado et al. 2010) exercise programs.

59.2.2 Exercise Is Effective for Psychiatric Conditions and Symptoms

Aerobic and resistance exercise interventions are useful for a wide range of psychiatric conditions, including anxiety and depression (Zschucke et al. 2013). The majority of studies have demonstrated efficacy of exercise in reducing symptoms of depression in both inpatient (Martinsen et al. 1985) and outpatient (e.g., McNeil et al. 1991) settings; favorable results have been highlighted in several review articles (e.g., Barbour et al. 2007; Martinsen 2008) and meta-analyses (North et al. 1990; Craft and Landers 1998). Exercise has been shown to reduce depressive symptoms in medically compromised populations, including cardiac (Pinto et al. 2013) and cancer (McLellan 2013) patients. The benefits of exercise relative to psychotropic medication (Blumenthal et al. 1999) and

psychotherapy (Greist et al. 1979; Klein et al. 1985; Fremont and Craighead 1987) have also been investigated; equivalent benefits have been found comparing exercise with medication, time-limited or time-unlimited psychotherapy, group therapy, and cognitive-behavioral therapy.

State anxiety has been shown to acutely diminish after individual episodes of exercise (Raglin and Morgan 1987), and aerobic exercise may confer significant benefit in the treatment of adults with moderate to severe panic disorder (Broocks et al. 1998; Ströhle et al. 2009) and obsessive compulsive disorder (Abrantes et al. 2009). The majority of studies have suggested efficacy of exercise in mitigating stress-related symptoms across a variety of study populations, including nonclinical (Lion 1978; Bahrke and Morgan 1978; Blumenthal et al. 1982), clinical (Abrantes et al. 2009), and medically compromised (Prosser et al. 1981) adults. In a study of adults with significant anxiety sensitivity, a 2-week exercise intervention significantly reduced anxiety sensitivity relative to no-treatment control (Smits et al. 2008), an effect which mediated the benefits of exercise on negative affect states including anxious and depressed mood.

Substance dependence is associated with elevated rates of comorbid psychiatric disorders, particularly depressive and anxiety disorders (e.g., Mason et al. 1998; Glasner-Edwards et al. 2008). Severity of psychiatric symptoms has been associated with poorer treatment outcomes in multiple prior studies (e.g., Rounsaville et al. 1986; Cacciola et al. 2001; Glasner-Edwards et al. 2009). Upon cessation of drug use, abstinence syndromes comprising prominent psychiatric features may emerge (e.g., McGregor et al. 2005). Syndromes may be characterized by drug cravings coupled with marked depressive symptoms including anhedonia, dysphoria, irritability, poor concentration, hypersomnia, low energy, and even suicidality (Meredith et al. 2005). The contribution of emotional stress to drug use and relapse has been well documented (e.g., Sinha et al. 2006; Fox et al. 2007; Tate et al. 2008), and considerable evidence is accumulating to suggest that substance abusers exhibit deficits in their ability to process and regulate such stress.

59.2.3 Exercise Improves Cognition

Cognitive deficits have been observed in long-term users of various substances. Chronic opioid use, for example, is associated with deficits in attention, processing speed, working memory, and executive functions (Mintzer and Stitzer 2002) that can negatively impact methadone treatment response (Davis et al. 2002). Methamphetamine users suffer from cognitive impairments during initial months of abstinence, including working memory, selective attention (Simon and Domier et al. 2002), learning (Gonzalez and Rippeth et al. 2004), and decision-making (e.g., Bechara and Damasio 2002; Paulus et al. 2003). Deficits in multiple cognitive domains have been observed in alcohol-dependent individuals, including impairment in visuospatial and perceptuomotor functions, executive functions, and short-term memory in addition to dementia and Korsakoff syndrome (Kopera et al. 2012).

Meta-analyses of randomized, controlled trials confirm that normal and cognitively impaired adults derive cognitive benefits from physical exercise (Etnier et al. 2006; Colcombe and Kramer 2003; Heyn et al. 2004; Angevaren et al. 2008). Improvements are the greatest for executive control processes (e.g., planning, scheduling, working memory, dealing with distraction, multitasking), for participants in combined strength and aerobic training regimens, and when exercise duration is greater than 30 min (Colcombe and Kramer 2003). Angevaren et al. (2008) found largest effects of aerobic exercise on motor and auditory function, and moderate effects were observed for cognitive speed and visual attention. Executive and other cognitive functions have been shown to improve after acute bouts of resistance exercise in middle-aged adults (Chang et al. 2013).

Exercise may hasten or improve recovery from substance dependence by contributing effects on underlying neurobiological processes, such as dopamine activity (Robertson et al. 2012). A recent study demonstrated reversal of methamphetamine-induced striatal dopamine transporter and tyrosine hydroxylase damage after exercise in rodents (O'Dell et al. 2012). In addition, neurotrophic proteins may be regulated in part by exercise and play an important role in regulating neuronal function in the brain and help to sustain normal cognitive, emotional, and behavioral functioning. Brain-derived neurotrophic factor (BDNF), the most widely expressed neurotrophin in the brain, supports synaptic plasticity, facilitates neurogenesis, and modulates neurotransmission (de Cid et al. 2008).

An emerging literature suggests that BDNF may have a role in the pathogenesis of addictive disorders (Heberlein et al. 2011). Treatment interventions that affect BDNF production may mediate synaptic plasticity and neuroprotection, which could in turn ameliorate negative affective symptoms, impulsivity, and other cognitive deficits associated with ongoing drug use and relapse risk. Exercise, for example, has been shown in preclinical (Russo-Neustadt et al. 2000; Seifert et al. 2010) and human (Ploughman 2008) studies to enhance BDNF release in the brain. This is potentially significant because of the purported benefits of exercise on cognitive functioning (Neeper et al. 1995); cognitive deficits have been observed in chronic substance abusers as evidenced by poor performance on memory and attention tasks and learning deficits (Cipolli and Galliani 1987; Guerra et al. 1987). Substance dependence is also associated with poor impulse control and selective processing (Lundqvist 2005). In addition, exercise has been shown to ameliorate negative mood states that may contribute to substance relapse, and prior literature has suggested that low BDNF levels in individuals with substance dependence may predispose to higher rates of psychiatric comorbidity (Angelucci et al. 2007).

59.2.4 Exercise for Reducing Substance Use and Preventing Relapse

An emerging literature on exercise-based interventions for substance use disorders provides preliminary evidence in support of this approach. In a study of cocaine-addicted rodents, rats given access to aerobic activity demonstrated reduction in

cocaine seeking relative to those who did not have access to such activity (Lynch et al. 2010). The majority of clinical research has focused on aerobic exercise as a potential intervention to aid smoking cessation and has shown mixed effects of exercise on smoking abstinence; more consistent positive effects on cigarette cravings, withdrawal symptoms, and smoking-related behaviors after exercise sessions have been demonstrated (Taylor et al. 2006). In an investigation of women enrolled in a 12-week cognitive behavioral smoking-cessation program, subjects were randomized to receive either vigorous aerobic exercise or health education three times a week (Bock et al. 1999). Those who participated in the exercise group evidenced significant reductions in cigarette craving, negative affect, and nicotine withdrawal during most weeks of the program.

More recent observational studies have suggested a preliminary positive effect of exercise in reducing substance use in both treatment-engaged substance users (Brown et al. 2010) and in nontreatment-seeking cannabis users (Buchowski et al. 2011). In the treatment population, it was noted that substance use outcomes were significantly better among substance users who attended at least 75 % of exercise sessions (Brown et al. 2010). An 8–9-week structured exercise program has also demonstrated efficacy in adolescents enrolled in drug treatment programs; adolescents who improved in self-concept, anxiety, and depression risk factors reported reduced substance use relative to those who did not improve on similar measures (Collingwood et al. 1991). Similarly, a prospective investigation of more than 4,000 twins revealed lower rates of illicit drug use and alcohol use consequences in adulthood among physically active adolescents, supporting prior work suggesting a relationship between low physical activity in adolescents and drug use (Korhonen et al. 2009).

In addition to our ongoing study described below, a multisite study is being conducted in the United States by the Clinical Trials Network (CTN), funded by the National Institute on Drug Abuse, investigating the benefits of an exercise component added to residential programs addressing stimulant use disorders. The CTN0037 trial, Stimulant Reduction Intervention Using Dosed Exercise (STRIDE), is a randomized controlled trial to test the effectiveness of the addition of exercise compared to health education to treatment as usual in improving drug treatment outcomes in 330 participants with DSM-IV-diagnosed stimulant abuse or dependence (e.g., cocaine, methamphetamine, amphetamine) and receiving treatment in residential settings; conditions include either Vigorous Intensity High Dose Exercise Augmentation (VIHD) plus Usual Care or Health Education Intervention Augmentation (HEI) plus Usual Care.

59.2.5 Study of Exercise as an Intervention for Methamphetamine Use Disorders

As indicated in the brief review of the literature, an exercise regime may be useful in addressing craving, mood states, and resultant drug-seeking behavior that can lead to relapse. To explore the effectiveness of exercise for stimulant use disorders,

Dr. Richard Rawson and colleagues at the University of California, Los Angeles, are conducting an investigation of the utility and efficacy of an 8-week, evidence-based aerobic and resistance exercise intervention to promote improved treatment outcomes for a sample of 150 individuals in residential treatment for methamphetamine dependence. The study is examining medical, psychiatric, neurocognitive, and behavioral benefits that may accrue during participation in an 8-week exercise intervention, as well as possible sustained beneficial impacts on drug use following completion of the exercise protocol and discharge from the residential treatment program. The project also includes a brain imaging component to collect data leading to an improved understanding of the mechanisms that may underlie observed effects on treatment outcomes and symptom remediation associated with the exercise intervention.

Methamphetamine-dependent individuals are screened to determine eligibility, and those randomized to the exercise intervention participate in supervised progressive endurance and resistance training three times per week for 8 weeks (24 sessions) consistent with current guidelines for comprehensive exercise programs (American College of Sports Medicine [ACSM] 2000). Each session consists of a 5-min warm-up, 30 min of aerobic activity on a treadmill, 15 min of resistance training, and a 5-min cooldown with stretching and light calisthenics. The goal of the aerobic training is to accumulate at least 30 min of continuous aerobic exercise at a target intensity set by data derived from maximal incremental exercise testing as described below. Information derived from the incremental testing is also used to define a safe ceiling for exercise intensity for each participant. The goal of the resistance training is to develop adaptations in muscle strength and body composition to complement the aerobic training program. A total of nine exercises are performed each day for major muscle groups.

Participants randomized to the control condition participate in a health and wellness education session three times a week for 45 min. A counselor provides informational materials, facilitates discussion of educational content, monitors attendance, and documents participants' involvement. Sessions consist of an integrated multimedia educational program addressing a variety of health, wellness, and lifestyle topics such as nutrition, dental care, acupressure, sleep hygiene, and health screening, adapted from a previously implemented wellness manual used by Kinnunen et al. (2008).

All study participants complete a maximal incremental exercise test (XT) on a treadmill ergometer using a symptom-limited incremental protocol with linear increases in the work rate with respect to time (Cooper 2001). This test occurs three times during participation – at baseline, study week 5, and immediately following the intervention phase or upon intervention termination. Aerobic capacity $\left(\dot{V}O_2\text{max}\right)$ and the metabolic or lactate threshold $\left(\dot{V}O_2\theta\right)$, which is the level of oxygen uptake that defines one's ability to perform prolonged work, are measured using indirect calorimetry with an automated metabolic measurement system. The $\dot{V}O_2$max and $\dot{V}O_2\theta$ are used as baseline markers of aerobic fitness as well as for objective indices of each individual's tailored aerobic exercise intervention.

Participants undergo further fitness assessments to determine baseline body composition (skinfolds), muscle strength by 1-repetition maximum (1-RM) for leg press and chest press, and muscle endurance (repetitions to failure using 85 % of their leg press and chest press 1-RM values). The 1-RM represents the maximum weight that can be lifted only once through a complete range of motion. The 1-RM and muscle endurance test data are used to establish baseline values of muscle strength and endurance in the study population and to help guide the development of the individual-tailored resistance training exercise program (NSCA 2010). This test is administered at baseline, week 5, and upon intervention termination. Data obtained from the body composition analysis enable tracking of changes in fat mass and, importantly, changes in the fat-free mass and skeletal muscle mass. These data are obtained using standard skinfold and girth measurement techniques (Lohman et al. 1991) and calculated using the Jackson and Pollack equation (Jackson and Pollock 1978) and MRI-validated equations, respectively (Lee et al. 2000).

A subset of consenting participants (15 from each condition) undergo two positron emission tomography (PET) sessions and two magnetic resonance imaging (MRI) sessions before commencement of the experimental condition and again after the 8 weeks of intervention. Brain region volumes will be determined for subcortical regions including the caudate, putamen, and nucleus accumbens. Dopamine D_2/D_3 receptor availability will be calculated as binding potential (BP_{ND}) using the D2/D3 ligand [(18)F]fallypride. The MRI scan will be used to confirm the absence of structural brain lesions and to aid in localization of volumes of interest.

59.2.6 Preliminary Results from the Exercise Study

Preliminary data from the study based on the 123 participants randomized by the time of this writing suggest that methamphetamine users can safely engage in exercise and can derive significant health benefits over a short period. Data from the first 29 study completers, randomized to either exercise (EX, $n = 15$) or health education (ED, $n = 14$), were analyzed to evaluate exercise-related physical outcomes, including aerobic fitness, body composition, and muscle strength. EX subjects significantly improved maximum oxygen uptake by 0.63 ± 0.22 L/min (21 %), leg press (LP) strength by 24.4 ± 5.6 kg (40 %), and chest press (CP) strength by 20.6 ± 5.7 kg (49 %). For EX subjects, LP and CP endurance improved by ten repetitions (120 %) and seven repetitions (96 %), respectively, and these changes were significantly greater than those seen in ED. Changes in body composition for EX subjects included significant reductions in body weight (average 1.7 ± 2.4 kg, 2 %), % relative body fat (2.8 ± 1.3 %, 15 %), and fat weight (2.8 ± 1.8 kg, 18 %). None of these variables changed significantly in participants receiving ED (Dolezal et al. 2013).

Preliminary data collected from 50 participants revealed an increase in heart rate variability in individuals who participated in the 8-week exercise program, but not in individuals randomized to the health education control group. Heart rate

variability reflects the ability of the autonomic nervous system (ANS) to adapt quickly to stress and changes in the environment and is diminished in stimulant users (Dolezal et al. 2013). In addition, preliminary results from the PET and MRI neuroimaging examination of a subset of participants suggest improvement in dopamine receptor binding after participation in the exercise program. Study participants in the EX condition demonstrated improvement in D2/D3 binding after 8 weeks of exercise according to analysis of PET (using ^{18}F-fallypride); matched outpatient controls did not demonstrate increased dopamine receptor binding after 4 weeks of abstinence only (Robertson et al. 2012).

59.3 Conclusion

Exercise may be a useful approach to aiding individuals with substance use disorders in their efforts to avoid relapse after they have achieved abstinence via treatment. The addition of a new, non-drug-related activity may provide a reinforcing alternative behavior that may be effective in facilitating abstinence by enhancing positive mood states via effects of exercise on the endogenous opioid system and potentiation of dopaminergic transmission (Meeusen 2005). Prior literature demonstrates that exercise can improve anxiety and depression, symptoms that are often associated with initial phases of abstinence after cessation of drug use. Such conditions predispose individuals to relapse and predict poorer treatment outcomes (e.g., Nunes and Levin 2004; Poling et al. 2007). Exercise also improves sleep (Youngstedt 2005) and performance on cognitive tasks, which may be impaired in chronic substance users. In light of the documented associations between stress, negative affect, and substance relapse in addicted populations (Breslin et al. 2002; Marlatt 1996), together with evidence demonstrating stress regulation deficits in substance users, the development of interventions to ameliorate symptoms of depression and anxiety and improve affect regulation may help to reduce relapse risk in this population. Relief of distressing psychological symptoms may serve to complement relapse prevention skills taught in common therapy approaches for substance users and to promote health and positive behavioral changes consistent with treatment goals.

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Computerized Therapies: Towards an Addiction Treatment Technology Test

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Abstract

Information technology is broadly influencing many aspects of modern life, including the activities of healthcare users and providers. As part of this evolution,

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opportunities for utilizing technology are being realized and evaluated in the field of addiction. This chapter reviews progress toward achieving the goals of an Addiction Treatment Technology Test that comprises development of technological applications that advance the addiction treatment delivery system by facilitating better access to care, improving efficiency of treatment delivery, enhancing treatment outcomes, proliferating the translation and implementation of evidence-based interventions, and fostering implementation of cost-effective care. The chapter provides an overview of the types of treatments that have been adapted for technology delivery, a review of studies that have evaluated computer- and Web-based programs, and examples of innovative technology-based applications designed to supplement or enhance traditional psychosocial therapies. We synthesize these findings into general conclusions recognizing the limitations of current knowledge. We additionally discuss the prospects for current use and future possibilities. Understanding optimal models of deployment of addiction treatment may be particularly important in light of evolving healthcare systems (such as those evolving under the Affordable Care Act in the USA). We view the future optimistically and anticipate that continued research exploring novel aspects of addiction and its treatment will reveal interventions that can be effectively deployed using innovative technological approaches. Such technologies can clearly extend the reach of our interventions, which will contribute to improving the lives of those suffering from problems related to addiction.

60.1 Introduction

In the landmark paper published in 1950, "Computing Machinery and Intelligence," Alan Turing asked whether technological devices could exhibit intelligence that was indistinguishable from a human (Turing 1950). According to Turing, the test of achieving this goal would consist of one person conversing putatively with another unseen person and stating that he or she was interacting with another human when, in fact, the other member of the dyad was a computer. This test, often referred to as the Turing test, set the stage for important developments in science (Crick and Koch 2003), new philosophical domains (Boden 1990), a vast stream of science fiction novels (e.g., Stephenson 1995), and continued efforts to develop more humanlike computers and computer programs (e.g., Kurzweil 2012).

Since Turing first framed this challenge, the revolution in information (computer and telecommunications) technology has broadened the scope of what technology can contribute to society far beyond simple machine replacing human considerations. Consider, for example, the amazing fact that there are approximately six billion mobile phone subscriptions worldwide (ITU 2011), while the world's population is a little over seven billion (US Census Bureau 2013). The market penetration of these and related information-based technologies – irrespective of whether they are mobile phones, smartphones, tablet computers, or wireless local areas networks – is rendering a world where information technologies are both more accessible and affordable. Not surprisingly, information technology is

Table 60.1 Potential benefits of various technology-delivered interventions

Facilitate **easier access** to treatment for patients
Allow patients **concurrent access** to treatment, not dependent on therapist availability
Reach patients with **difficulties accessing in-person treatment** (e.g., rural residents, lack of transportation, social anxiety)
Ease the burden associated with therapist training
Ensure integrity and fidelity of treatment delivery
Promote **easier and more rapid dissemination and adoption** of evidence-based treatments
Reduce cost of treatment delivery by reducing therapist time
Facilitate resource reallocation to:
Match treatment to patient need
Facilitate adoption of effective interventions like abstinence-based contingency management programs
Better allocate therapist time to cases or issues requiring specific skills (e.g., dual diagnosis, cognitive deficits, crisis intervention)
Enhance learning and practice of therapeutic information and skills via use of active learning technologies and modalities
Increase access to therapeutic materials (accessed anytime/anywhere through the Internet)
Prompt use of therapeutic skills between clinic visits and post treatment
Increase access to social support through various types of social media
Enhance motivation through scheduled messaging and other tools
Increase probability of active coping with triggers or lapses through automatic or scheduled prompting
Facilitate monitoring of target behavior necessary for implementation of Contingency Management

broadly influencing many aspects of modern life, including healthcare. For instance, a recent review of health information technology (Goldzweig et al. 2009) has identified two major trends. First, an increasing number of commercial electronic health records are available that could foster the continuity of care for patients. Second, and most relevant to this chapter, is the proliferation of patient-focused applications. Such applications include those that (a) are directly accessed by the patient with no professional input, (b) provide a medium to interact with a professional remotely (telephone, videoconferencing), and (c) provide systematic behavioral interventions with minimal to moderate oversight by health professionals. The authors note that these programs putatively "increase efficiency (text-message appointment reminders, Internet-based cognitive behavioral therapy), . . . improve quality (Web-based diabetes management), and . . . provide more accessible care for difficult-to-treat problems (alcohol abuse and eating disorder sites)" (p. 291). Also, they note that these programs often have not been evaluated. These advances are highly welcome, given that difficulty in accessing state-of-the-art or specialty care can result in failure to obtain effective treatment for disease processes while they are still tractable. Yet as important as this expansion in program availability is, equally important is the efficacy of these programs.

The use of technology has many potential benefits for the patient and the provider (see Table 60.1). For patients, treatment delivered via information technology could enhance access in at least three ways. First, technology-delivered treatment does not have limitations in the number of patients seen per unit of time. As such, technology-delivered

treatment can avoid the challenges of waiting lists and can be used by countless numbers of individuals concurrently. Second, technology-delivered treatment can be accessed where the patients live, even if they live in rural or other environments that make the commute to treatment difficult. Third, this type of treatment needs not be restricted to office hours or provider availability. Therefore, this treatment is available in principle all the time and potentially for greater durations of time. Another benefit for patients is that by not directly interacting with a human change agent, they may find it easier to address sensitive issues, such as addiction and other related topics like HIV status, as suggested by several studies (Kobak et al. 1996; Marsch and Bickel 2004).

For the provider of care, there are at least three benefits. First, technology-delivered treatment has the potential to dramatically lower costs; that is because even in hybrid models where therapists also participate and monitor the use of technology-based treatment, less therapist time would be required per case (e.g., Bickel et al. 2008; Budney et al. 2011). Second, treatments that are delivered via technology will be conducted with fidelity. One reason for the loss of efficacy of providing evidence-based treatments in many community-based systems of care is that the treatment is provided without being faithful to intended procedures, which, in turn, renders the treatment both not evidence based and less likely to be effective. Third, providing treatment via technologies permits new scientific information to be rapidly and continuously incorporated into contemporary treatment without the effort and expensive task of training therapists in each novel innovation. Collectively, these and other potential benefits provide a strong case for incorporating this novel approach into routine care.

Fortunately, opportunities for optimally utilizing technology have begun to be realized and evaluated in the field of addiction. Given this increased activity in the space of technology-delivered treatment for addiction, we can consider what might constitute a modern-day Turing test, perhaps labeled the Addiction Treatment Technology Test. This test would consist of the development of technological applications that advance the addiction treatment delivery system by facilitating better access to care, improving efficiency of treatment delivery from both the patient and provider perspective, enhancing treatment outcomes, proliferating the translation and implementation of evidence-based interventions, and fostering implementation of cost-effective care. We hope that the posing of an Addiction Treatment Technology Test, like the framing of the Turing test, will prompt the development and improvement of information technology as related to such therapeutic ends.

In this chapter, we review the current status and postulate future directions of technology-delivered treatments for substance use disorders. In doing so, we first briefly review and describe the types of treatments that have been adapted for technology-delivered treatment. Second, we concisely review those studies that have evaluated computer- and Web-based programs. Third, we provide examples of innovative technology-based applications designed to supplement or enhance traditional psychosocial therapies. Finally, we synthesize the findings into general conclusions with recognition of the limitations of current knowledge, prospects for current use, future possibilities, as well as assessment of the status of the field with respect to the Addiction Treatment Technology Test.

60.2 Technology Development, Testing, and Application

60.2.1 Psychosocial Interventions and Their Translation to Technology-Based Delivery

60.2.1.1 Evidence-Based Psychosocial Interventions

Behavioral or cognitive behavioral interventions are the most common types of psychosocial therapies used to treat substance use problems that have been subjected to empirical evaluation in controlled studies. They, in addition to a number of pharmacotherapies, are typically considered as representative of the majority of the evidence-based treatments for substance use disorders. No universal definition exists for what comprises a behavioral treatment or an evidence-based intervention. Thus, this chapter will focus on psychosocial therapies that have received empirical support in clinical trials, been translated for computer- or Web-based delivery, and then been tested in controlled studies.

Four psychosocial approaches meet these criteria. **Motivational enhancement therapies (MET)**, based on the principles of motivational interviewing, use a client-centered, semi-directive approach to facilitate active change by assisting individuals in exploring and resolving ambivalence about change, setting individualized goals, and promoting self-efficacy about their ability to change. MET provides a very brief (one to four sessions) course of treatment that involves a very specific, nonjudgmental counseling style designed to lead the individual to set clear goals and take action toward change without providing prescriptive instruction or skills training. MET has been studied as a stand-alone intervention and has also frequently been combined with other approaches, most frequently with CBT. **Cognitive behavioral therapies (CBT)** have received empirical support in multiple trials across most substance use disorders. Multiple names have been used to describe highly similar types of CBT, such as coping skills training, relapse prevention, and MATRIX. All these approaches include psychoeducation about a cognitive behavioral model of substance use, teaching and practice of skills related to achieving abstinence or reduction in use, general coping skills training to strengthen alternative coping behaviors to substance use and to support lifestyle modification, and teaching of skills to help maintain abstinence and deal with lapses or relapses.

The community reinforcement approach (CRA) focuses on behavioral analytic model of substance abuse, focusing on encouraging behavior that can increase nondrug sources of reinforcement (e.g., gainful employment, participation in prosocial recreational activities, improving relationship quality) that can compete with drug use in addition to providing many common elements of CBT. **Contingency management (CM)** interventions utilize the basic principles of behavior analysis to systematically use reward or punishment to obtain targeted changes in behavior. Incentive-based CM targeting drug or alcohol abstinence or other therapeutic behavior (e.g., treatment attendance, participation in recreation or vocational activities, medication compliance) has received much empirical support over the past 20 years.

60.2.1.2 Computer/Web Translations of Evidence-Based Interventions

CBT/CRA

One of the earliest demonstrations of translating a CBT-type intervention for computer delivery tested a smoking cessation program developed for and completely delivered on the CompuServe computer network (Schneider et al. 1990). Self-selected participants ($n = 1{,}158$) signed on to the program after viewing an advertisement. They then completed an online consent and were randomized to four conditions: (1) a computerized smoking cessation program plus a stop smoking online forum, (2) the program without the forum, (3) a sham program with the forum, and (4) a sham program without the forum. This program was available for 6 months, 24 h a day, and had a menu of "modules" that guided the participant to set a quit date and provided instructions for using CBT-type strategies for initiating and maintaining quit attempts, dealing with urges, and coping with common problems, and it also showed a progress graph. The forum provided a place where participants could view others' written comments related to quitting and the program. The active program engendered significantly better smoking abstinence rates at 1 and 3 months than the sham program, with no significant effect observed for the online forum. Of note, no difference between the active and sham conditions was observed at a 6-month follow-up, and, generally, the active use of the programs was considered poor (only 9 % used the program for more than 3 weeks).

A program to deliver an effective treatment for mild to moderate alcohol problems, Behavioral Self-Control Training (BSCT), using an early Windows application was evaluated in a trial using a randomized, wait-list control design (Hester and Delaney 1997). Twenty heavy drinkers received 8 weekly, computerized BSCT sessions at a treatment clinic immediately after a pretreatment assessment; the other 20 participants received the treatment after a 10-week waiting period. The program instructed the participant on goal setting, self-monitoring of drinking, drink refusal skills, evaluating and coping with triggers, functional analysis, and relapse prevention. Both the immediate and delayed treatment conditions resulted in significant reductions in drinking with pretreatment levels averaging 35.2 and 42.2 drinks per week, respectively, and 12-month follow-up levels averaging 14.5 and 23.0 drinks per week, respectively. Note that the delayed group's reduction was not initiated until they received BSCT.

More recently, a more complex software program, the Therapeutic Education System (TES), translated CRA and CBT components to an interactive, Web-based delivery platform and evaluated its initial efficacy in trial of opioid- and cocaine-dependent outpatients (Bickel et al. 2008). The TES includes over 65 interactive, multimedia modules focused on basic CBT skills, skills to increase psychosocial functioning (e.g., employment status, family/social relations, financial management, communication, decision-making, management of negative moods, time management, and recreational activities) and, skills to assist in the prevention of HIV, hepatitis, and sexually transmitted infections. TES uses a number of types of informational technology to assist in the teaching and practice of these skills.

Programming utilizes a fluency-based teaching approach to continually assess (via interactive quizzes) a participant's understanding of the material and adjusts the pace and level of repetition to promote learning of the information and mastery of the skills. An experiential learning environment is also created via the use of interactive videos of actors modeling various behaviors to promote learning through the modeling. Interactive exercises enhance learning (e.g., graphics and animation) and personalize content (e.g., personalized functional analysis). TES can also facilitate CM programs with a flexible system for tracking and reinforcing target behaviors (e.g., abstinence) and monitoring incentive earnings (see more on this in the CM section below). Last, TES can provide therapists access to summaries of patient TES activity and progress, facilitating integration of TES activities with counseling sessions.

The initial efficacy trial of TES-delivered CRA/CBT involved 135 opioid and cocaine dependent patients seeking treatment at a buprenorphine clinic (Bickel et al. 2008). Participants were randomized to one of the three 23-week programs: (1) TES sessions three times per week with biweekly counselor contact and incentives (CM) for abstinence, (2) therapist-delivered CRA/CBT with incentives for abstinence, or (3) standard drug counseling. Abstinence outcomes for cocaine and opioids did not differ between the TES-delivered and therapist-delivered conditions (mean weeks of continuous abstinence: 7.9 and 8.0, respectively), and both these CRA/CBT conditions were superior to standard counseling (4.7 mean weeks of abstinence). TES- and therapist-delivered CRA/CBT also engendered comparable outcomes on measures of treatment retention, Addiction Severity Index scores, and therapeutic alliance with their counselor. The TES reduced time spent with counselors by 80 %, with a concomitant estimated reduction in cost of over 70 %. Another trial evaluated this TES program for methadone-maintained patients in the context of better understanding the relationship between cognitive functioning and treatment outcome (Acosta et al. 2012). TES-delivered care enhanced abstinence outcomes for patients with lower cognitive functioning when it partially substituted for standard counseling, suggesting that the learning technologies and self-paced aspect of TES may help attenuate the usually observed negative impact of lower cognitive function on substance use treatment outcomes.

Another innovative, six-session program, computer-based training in CBT (called CBT4CBT) uses videotaped vignettes to illustrate the CBT skills taught within the program, focusing on (1) understanding and changing patterns of substance use, (2) coping with craving, (3) substance refusal skills, (4) problem-solving skills, (5) identifying and changing thoughts about substances, and (6) improving decision-making skills (Carroll et al. 2008). An initial randomized efficacy trial compared outcomes for 77 adults entering outpatient treatment for various types of substance dependence. Participants received an 8-week course of either weekly standard care (individual and group drug counseling) or standard care plus CBT4CBT delivered via a computer in a private office in the clinic. CBT4CBT participants achieved more drug abstinence than those in the standard-only condition (66 % vs. 47 % negative urine samples). Six-month follow-up assessments continued to show significantly better drug use outcomes for CBT4CBT, indicating

that the positive effects endured over time (Carroll et al. 2009). There were statistically significant increases in mean ratings of the quality of participants' coping responses for those assigned to CBT4CBT compared to treatment as usual, and these differences remained significant 3 months after treatment completion. Moreover, quality of coping responses mediated the effect of treatment on participants' duration of abstinence during the follow-up period (Kiluk et al. 2010). Last, the clinic cost of adding CBT4CBT approximates just $39 per participant (Olmstead et al. 2010).

MET and MET/CBT

Early efforts to translate the content and practice of MI or MET for delivery via computer were manifested in the Drinker's Check-Up (DCU), developed as both a Windows and Web-based application (Hester et al. 2005). This program integrates a computerized substance use-related assessment module with personalized feedback and decision-making modules. This self-directed program provides most of the active components of MET: provide personalized feedback, assessment of motivation to change, develop discrepancies using decisional balance exercises, negotiation and acceptance of personal goals, development of a change plan, and information on alternative sources of help related to goals. Sixty-one adults with mild to severe alcohol problems were randomly assigned to receive the one-session, 90-minute DCU immediately or after a delay of 1 month (wait-list control design). Participants completed the DCU on a computer at the clinic. Various quantity and frequency of drinking measures and alcohol problem score outcome showed significant reductions with large effect sizes in both groups at 1-month post DCU and at a 12-month follow-up.

A Web-based version of the DCU was evaluated in a large convenience sample of active duty military personnel (Pemberton et al. 2011). Compared with those randomized to a no-intervention control condition, DCU reduced quantity and frequency measures of drinking at a one-month follow-up, and this reduction was maintained at 6 months. A version of the DCU adapted for use with heavy drinking college students was evaluated in two studies: one trial used a similar wait-list control design, and one compared it to an assessment-only condition (Hester et al. 2012). Results from both studies supported the efficacy of the DCU for reducing heavy drinking in this at-risk population.

Another MET-based computerized intervention [Motivational Enhancement System (MES)] was designed for postpartum women who reported drug use before pregnancy (Ondersma et al. 2005). Similar to the DCU, the MES delivered three primary components during one session: (1) personalized feedback, (2) evaluation of pros and cons of drug use and related change, and (3) exploration of readiness to change and related goal setting. The initial evaluation of MES involved randomization of 30 women either to the MES or to an assessment-only control group. The assessments and MES were completed in their hospital rooms on laptops with an integrated touch screen. MES engendered greater levels of motivation to change drug use, but no differences between conditions were observed on self-reports of drug use. A subsequent study, using the same experimental design, extended the

initial findings with 107 postpartum women (Ondersma et al. 2007). More reduction in self-reported indicators of illicit drug use (nonsignificant effects, but mild to moderate effect sizes) was observed for the MES participants at a 4-month follow-up. The MES has been adapted and piloted for alcohol reduction in pregnant women (Tzilos et al. 2011). This same research group adapted the MES for smoking using the 5-As brief intervention model for smoking cessation and tested it in combination with a CM incentive program (also computer assisted: Ondersma et al. 2012). Findings from this study of 110 pregnant smokers suggested that the computerized 5-As program improved abstinence and increased discussion with a health professional about smoking cessation.

The TES program described above was modified to add an MET component similar to the DCU in an initial study of outpatient treatment for cannabis use disorders (Budney et al. 2011). Parallel, nine-session MET/CBT therapist- and computer-delivered programs were compared in an initial quasi-experimental trial in which both groups also received abstinence-based CM. The computerized condition also involved three brief supportive therapy sessions. Cannabis use and abstinence outcomes did not differ between conditions during treatment, and no differences were observed on other secondary outcomes such as problems related to marijuana, self-efficacy, or use of coping skills strategies. The mean amount of therapist time per case was approximately tenfold greater in the therapist-delivered condition, suggesting substantial cost savings associated with the computerized MET/CBT. Preliminary findings reported from a second trial replicated and extended these findings, suggesting that the computer- and therapist-delivered MET/CBT showed comparable outcomes both during treatment and throughout a 12-month follow-up period.

A research group from Australia developed a similar computer-delivered CBT-type program to treat cannabis or alcohol problems *and* depression (Kay-Lambkin et al. 2009, 2011). This eight-session program focuses on the usual CBT skills, using a motivational interviewing (MI) style to interact with the participant related to goal setting and change planning. It concurrently provides content underscoring the relationship between substance misuse and depressive symptoms. In a randomized trial, 97 adults with major depressive disorder and problems with alcohol or cannabis use first received a one-session, brief MI interview targeting depressive symptoms and substance misuse followed by one of three conditions: (1) no further treatment, (2) nine sessions of CBT/MI delivered by a psychologist, or (3) nine sessions of CBT/MI delivered by a computer with concomitant 10–15 check-in sessions with a therapist at the end of each session. Acceptability, treatment retention, and therapeutic alliance did not differ between the CBT/MI conditions. The CBT/MI conditions produced better cannabis, alcohol, and depression outcomes than the brief intervention alone. The computerized intervention showed the largest effects on substance use outcomes. The therapist-delivered CBT showed better short-term outcomes on depression, but similar outcomes to the computer condition at 12 months.

A larger replication trial compared the same two CBT/MI conditions and a ten-session supportive, person-centered therapy (PCT) (Kay-Lambkin et al. 2011).

Both CBT/MI conditions produced superior alcohol and depression outcomes compared with PCT, and computer-delivered CBT/MI was associated with greater reductions in alcohol than the therapist-delivered CBT/MI. No significant differences were observed for cannabis outcomes, although reductions favored the two CBT/MI conditions. Of note, the computerized intervention required only 16 min on average of therapist time compared with 57 min for therapist-delivered CBT/MI, and unlike the therapist-delivered model, it did not require a clinician trained to deliver CBT/MI.

60.2.1.3 Contingency Management (CM)

An Internet-based, automated program was developed to increase access to an abstinence-based reinforcement CM program for tobacco smoking cessation (Dallery and Glenn 2005). Instead of coming to a clinic to provide objective evidence of smoking abstinence via carbon monoxide breath sampling, a Web-based software program (i.e., Motiv8 Systems™) enables participants to video themselves at home self-administering a carbon monoxide (CO) test via a webcam. Twice per day the participant videos and records the result (i.e., the display on the CO device), which is then delivered to the "treatment team" via the Internet. The video clips shows the CO monitor being reset, the participant exhaling into the monitor, and the CO reading. Upon receipt of the evidence for smoking reduction or abstinence, Motiv8 electronically delivers incentive earnings via an email. A website that is always available to participants displays their incentive earnings and provides links to Internet vendors (e.g., Amazon) from which they can purchase items using their incentive earnings. Several small studies, mostly using within-subject reversal experimental designs, have demonstrated the efficacy of this CM intervention with adult heavy smokers (Dallery and Glenn 2005; Dallery et al. 2007), adolescent smokers (Reynolds et al. 2008), and adult smokers in a rural setting (Stoops et al. 2009). Creative, alternative models using Motiv8 have explored methods to increase the potential of dissemination. One study illustrated how collecting up-front deposits from participants that could be earned back by demonstrating successful tobacco abstinence may be an effective way to offset the cost of the incentive program (Dallery et al. 2008). Another study tested a model in which a small group of smokers work together through a Web-based discussion board integrated with the Motiv8 system (Meredith et al. 2011). Achievement of group smoking cessation goals is required to earn incentives. Ideally, participants provide encouragement and feedback to each other, which can putatively enhance the longer-term maintenance of the positive effects achieved with the abstinence incentives. This series of studies clearly demonstrates the potential efficacy of delivering a CM intervention remotely, which increases the possibilities for effective delivery of this potent intervention model.

The TES platform described earlier also includes programming to assist with the administration of CM programs (see Bickel et al. 2008; Budney et al. 2011). When participants log into their TES program, the initial screen displays their available incentive earnings, cumulative earnings, a graphic display of

cumulative drug testing results, and a place for messages (e.g., social reinforcement or encouragement). The data needed to provide this information can be either entered manually by staff or sent directly from a computer integrated with drug testing analyzers. Although this does not fully automate a CM program, it helps systematize delivery and eases staff burden associated with administering CM.

The Therapeutic Workplace (TWP) is a novel, employment-based treatment intervention that has considerable potential for promoting sustained abstinence from alcohol and drugs while simultaneously addressing some of their interrelated problems of poverty, unemployment, and homelessness. The TWP integrates an abstinence-based reinforcement (CM) program (using the Motiv8 platform) with a CM-based employment program. A sophisticated, Web-based training and employment system trains, hires, and pays participants to work each day, using behavior analytic principles of learning and reinforcement (Silverman et al. 2001, 2005). The application operates from a PC server that is networked with staff and participant workstations. TWP software establishes users with a bar-coded picture ID card. The program records each trainee's arrival time and determines whether the trainee arrived to work on time. On days in which urine collection is required, the software requests urinalysis results, and if required test results are negative, the software grants access to the workroom. Drug-positive results deny access. Computerized typing, keypad, and data entry training programs are delivered to all participants, who take placement tests to determine at which step to begin training. The software monitors performance and automatically moves participants through each step of the program as they meet the speed and accuracy requirements.

An Activities and Earnings section of the participant's home page displays earnings for the current day, account balance, and key parameters that can affect earnings. The Base Pay section shows the current day's base pay hourly rate, minutes spent out of the workroom, hours worked, hours that earned the base pay rate, and total base pay earnings. The Administrative section shows additional administrative pay. The Training section data on training activities, number of correct and incorrect responses, the amount earned completion bonuses (Bonus), and the earnings for each program. For participants who advance to paid operators, the Data Entry section includes information for all work batches completed on the current day including the pay rate, the number of errors and amount lost for each, and the total earnings. Each participant has an Inbox to receive files and messages. Purchases from earnings are requested and tracked through the software.

The TWP has demonstrated effectiveness across multiple controlled studies in diverse subpopulations of substance abusers including heroin- and cocaine-using treatment-resistant young mothers (Silverman et al. 2001, 2002) and unemployed injection drug and crack cocaine users (Donlin et al. 2008; DeFulio et al. 2009; Dunn et al. 2013), homeless alcohol dependent (Koffarnus et al. 2011), and opioid-dependent adults (Everly et al. 2011). Such strong empirical support for the TWP and its Web-based technology clearly demonstrates how a technology-based system can produce cost-effective, sustainable effects with great potential for dissemination.

60.2.2 Computerized Interventions for Related Problems

60.2.2.1 HIV Education

A prototype, text-only version of the TES programming was first employed in a study comparing computer-delivered and therapist-delivered HIV/AIDS education among 30 opioid-dependent, injection drug users (IDUs) receiving buprenorphine treatment (Marsch and Bickel 2004). The computer-assisted instruction incorporated fluency-building technology that requires a predetermined level of accuracy and speed in responding, which adjusts based on the participant's level of responding. The program also provides performance feedback and remediation for errors. Participants who received computer-based instruction learned significantly more information and retained significantly more of that information at a 3-month follow-up. Interestingly, the participants in the computer-based condition liked the teaching medium more, and more were interested in receiving additional HIV services than those in the therapist-delivered condition (80 % vs. 20 %).

A second randomized trial with adolescents enrolled in substance abuse treatment compared a one-session, small-group, infectious disease educator-delivered HIV and other sexually transmitted infection prevention program to an enhanced TES program added to the educator-delivered program (Marsch et al. 2011). Again, results indicated this Web-based program increased prevention knowledge and intentions to more carefully choose partners, and it was also perceived as more useful than the educator-delivered intervention provided alone. These findings are consistent with many other HIV and infectious disease prevention studies with other populations, indicating that computer-based or Web-based education comprises an effective method that is attractive to at-risk populations and cost-effective (Noar et al. 2011). Some evidence suggests that technology-delivered compared with human-delivered assessment and instruction can result in more accurate reporting of the sensitive information encompassing risk behavior and more engagement from the patient as it may be perceived as less threatening (Des Jarlais et al. 1999; Kurth et al. 2004).

60.2.3 Innovative Technologies to Enhance Effective Psychosocial Treatments

Exciting and innovative applications of diverse technological devices and platforms to supplement or deliver specific components of psychosocial interventions are either being contemplated for development and testing or are active in ongoing research projects. Below, we provide brief examples of applications that may become available in the near future.

First, programmed Short Message Systems (texting) could facilitate the use of CBT/CRA skills (Whittaker et al. 2012). A few of many possibilities for this include prompting relapse prevention activities at certain times of the day, delivering educational messages that enhance learning of skills, providing motivational messages that maintain efforts directed toward recovery activities, and offering

regular reminders of specific goals and planned actions. Providers and patients could together develop and program messages to be sent at specific times and as often as deemed useful. With cell phone ownership having become the norm, almost all patients could benefit from this type of intervention if it proves efficacious in supplementing CBT/CRA.

Second, smartphones (i.e., cell phones with computing ability), Internet connectivity, and in some cases global position systems (GPS), offer even more possibilities than utilization of SMS (Gustafson et al. 2011; Marsch 2012). Access to the Internet and the ability to run software applications (Apps) translate into capability for delivering the same types of psychosocial therapy programs described above for the personal computer, but with the added benefit of access anywhere at anytime. Capitalizing on the mobile dimension of smartphones and their GPS capability, researchers have begun to develop and test "warning" systems that prompt coping responses from the user when she or he goes somewhere designated as a high-risk environment. Similarly, GPS tracking could be used to increase monitoring capabilities such that, for example, parents could increase awareness of their teens' whereabouts, a common goal in family-based therapies or prevention programs. Another example under development is smartphone integration with wireless devices that measure physiological responses (e.g., indicators of stress or craving). Detection of specific responses would trigger an automatic communication with the phone that would prompt or deliver a therapeutic coping intervention (e.g., Boyer et al. 2010). These types of innovative uses of technology to enhance CBT/CRA interventions are only just beginning to be realized and tested.

Virtual reality (VR), i.e., computer-simulated experiences that utilize visual, auditory, tactile, or olfactory sensory features to facilitate active participation in simulated environments, offers another exciting possible method for augmenting the learning of behavioral coping responses to high-risk situations. VR can simulate realistic substance use environments and provide opportunities to practice skills consistent with successfully negotiating the risk situations without substance (Bordnick et al. 2011). Exposure therapies for specific phobias and posttraumatic stress disorder have effectively utilized VR to enhance outcomes (e.g., Gerardi et al. 2010; Meyerbroker and Emmelkamp 2010). Similar projects are under way in the substance abuse field that use VR to improve cue exposure therapies targeting reduction in cravings associated with specific environmental situations.

Last, video game platforms may offer another promising paradigm for supplementing CBT/CRA interventions (e.g., Raiff et al. 2012). Such games could provide a medium that includes modeling of coping skills via culture- and gender-relevant characters and environments and reinforcement of mastery and effective use of coping skills. The player would be faced with making decisions in various substance use or related situations that lead to "realistic" consequences. Advancing to higher levels or winning the game would require effective decision making and use of coping skills associated with refusal to use or responsible use of substances. Health behavior video games, including some that target prevention of substance abuse, are already a reality (Marsch et al. 2007a, b; Schinke et al. 2009).

60.2.3.1 Targeting Cognitive/Executive Function

Evidence has accumulated indicating that those with various substance use disorders compared with those without these problems, engage in more impulsive decision making whereby their choice behavior reflects desire for smaller more immediate reinforcers over larger delayed reinforcers (Bickel et al. 2011a). This putatively reflects the impulsive system of the brain dominating the executive system, a notion that has received increasing scientific support as an important component of the addiction process (Bechara 2005; Bickel et al. 2012). This theory has guided the development of neurocognitive remediation or executive function therapy that targets strengthening of executive function to increase self-control and reduce impulsive decision making. Computer-delivered programs offer such training through repeated reinforced practice of cognitive exercises requiring attentional focus, visual-spatial and verbal memory, abstract reasoning, and problem-solving skills. Initial studies demonstrated that cognitively impaired substance abusers showed improvements in cognitive performance and remained in treatment longer following such remediation training (Grohman and Fals-Stewart 2003; Grohman et al. 2006). A preliminary study with stimulant-dependent adults has demonstrated positive changes in delay discounting, a marker of impulsive decision making, following training focused on enhancing working memory (Bickel et al. 2011b). A second study of substance abuse patients showed improvements in measures of working memory, response inhibition, and decision making following completion of a systematic executive function training program (Alfonso et al. 2011). A third research report showed reductions in alcohol consumption among heavy drinkers when working memory was the only intervention (Houben et al. 2011). Another potential mechanism by which cognitive remediation may positively impact treatment outcomes is through improvement of the efficiency of cognitive behavioral therapies that require individuals to learn, remember, and apply specific skills in diverse situations (Pedrero-Perez et al. 2011).

60.2.3.2 Internet-Based Social Support

The ubiquitous ownership of cell phones, smartphones, and computers has made it possible to obtain social support for recovery from addictions through multiple mediums. Digital technology can provide almost immediate access to support, and provides and may increase utilization of support networks among those less likely to seek such assistance (e.g., socially anxious individuals, those living in remote geographic areas or without transportation). Applications might either enhance or substitute for traditional self-help groups or group therapies. Many self-help groups have now established live text and voice chat meetings through the Internet available most anytime. Such technology also allows individual or group interventions for substance use to include digital support networks through popular social networks (e.g., Facebook) or by establishing a unique network. One can envision many alternative therapeutic uses for such digital networks. They could greatly expand access to assistance with handling cravings or lapses, to opportunities to practice therapeutic skills, or to obtain ideas and information related to prosocial activities such as job opportunities or recreational events. Similarly, for those

whose family members are struggling with addiction, these networks would increase access to support, guidance, and skills training related to coping effectively with their child or spouse.

60.2.4 International Considerations

Although much of the research with technology-based computerized therapies for substance use disorders described above was conducted in the USA, the computer-delivered CBT-based intervention for comorbid cannabis and alcohol problems and depression was developed and evaluated by Kay-Lambkin and colleagues in Australia (Kay-Lambkin et al. 2009, 2011). We know of several additional ongoing evaluations of computerized interventions being conducted around the world. These include a Web-based self-help intervention, grounded in CBT and MET approaches to targeting cocaine use (called "Snow Control"), which is being studied in a randomized clinical trial in Switzerland (Schaub et al. 2011). Additionally, a study conducted in Amsterdam compared an online CBT/MET self-directed intervention targeting problematic alcohol use to an online CBT/MET intervention delivered via asynchronous chat with a therapist. Both showed greater effects on alcohol use than a wait-list control condition and generally showed comparable effects to one another (Blankers et al. 2011).

Perhaps the most frequent approach to leveraging technology in the delivery of health behavior interventions globally has been to deliver them via mobile devices. Due to increased globalization and the opening of economies, technology-based communication structures in many low- to middle-income countries have become increasingly strong in recent years. Over 90 % of individuals worldwide subscribe to mobile phone services, translating to nearly six billion worldwide mobile phone subscriptions (Union 2012). This rapid growth in access to mobile technologies has significant promise for bridging the digital information divide and reducing healthcare disparities that exist in many systems of care, including among vulnerable and underserved populations (Gibbons et al. 2011).

Mobile health approaches have been particularly helpful in settings that lack sufficient healthcare workers and financial resources and have high disease burden (Kayingo 2012). Although mobile devices have been applied to substance use disorders only to a limited extent in most countries, they have been applied extensively to the prevention and treatment of HIV, including among substance-abusing populations. Globally, much of this work has been conducted in India, South Africa, and Kenya (Deglise et al. 2012), and a number of mobile tools have been shown to be promising as part of HIV prevention interventions and in improving adherence to HIV treatment and viral load suppression among HIV-positive persons (Swendeman and Rotheram-Borus 2010; Horvath et al. 2012). Overall, the state of research in this arena suggests that mobile therapeutic tools offer promise to have a substantive impact on global healthcare broadly and may be similarly promising in targeting prevention, treatment, and recovery support for substance use disorders.

60.3 Conclusion

The brief review included in this chapter illustrates how the exploration of technology-delivered or technology-assisted therapies for substance use problems has been developing for some time, shows great promise, and is gathering momentum. The accumulation of data and knowledge has progressed to the extent that a "review of reviews" recently appeared in the literature and identified 9 meta-analytic and 13 qualitative reviews of technology-based interventions for substance use disorders (Litvin et al. 2013). This review concluded that "technology-based interventions for substance use problems are efficacious, but effect sizes are generally small to medium at best and treatment mechanisms remain largely unknown"; a conclusion that most would agree closely parallels the status of the majority of traditional therapist-delivered interventions.

Although research to date is promising, we have a long way to go to pass our Addiction Treatment Technology Test. Multiple studies have demonstrated that treatment models assisted by computer- or Web-based delivery of evidenced-based interventions (MET, CBT, CRA, CM) have the potential to improve access to care, reduce costs, and improve efficiency of treatment delivery. However, in order to advance the potential public health impact of this research, several areas warrant further investigation. Among these is the need for an expansion of research that embraces an implementation science framework in evaluating models for best integrating evidence-based technology-based innovations in diverse community settings, bringing value to all relevant stakeholders in a care setting, and promoting their sustained use. These models may include evaluation of technology-based therapeutic tools as supplements to standard care models, as tools that can replace a portion of "treatment as usual," or as stand-alone tools accessed outside of care settings. Results of such research offer the potential to generate knowledge regarding models for accelerating the process from research discovery in this arena to public health benefit.

A related area of inquiry that could greatly benefit the field is an expanded focus on economic analyses that parallel analyses of clinical effectiveness. An understanding of the cost-effectiveness and cost-benefit of technology-based interventions, and the conditions and deployment models under which they do/do not demonstrate cost-effectiveness and cost-benefit, is critical in efforts to scale up their deployment. Understanding optimal models of deployment may be particularly important in light of evolving healthcare systems (such as those evolving under the Affordable Care Act in the USA).

Further, another important area of future efforts is an increased research focus on the mechanisms of behavior change from technology-based interventions compared to traditionally delivered approaches. Given their "on-demand" availability and opportunities for personalization, technology-based interventions may impact the rate and nature by which health behavior change occurs. An increased understanding of the active ingredients and mediators of outcome from technology-based therapeutic tools can greatly enhance future efforts to optimize technology development efforts. This understanding could additionally aid the research field of

technology-based interventions to progress beyond direct adaptations of existing face-to-face interventions to better harness the dynamic potential of technology in collecting data about individuals in unprecedented ways and in real-time and in intervening at the exact moments when individuals may be maximally motivated and receptive.

The future of technology-delivered treatment in the addictions field will surely be substantial and important – a true advance. But we must keep that advance in its appropriate place within the field of addiction. As we noted above, to date, these technology-delivered treatments largely produce the same level of efficacy as traditional person-delivered treatments that they are based upon. From this, we can consider at least three possibilities. First, we could make a pessimistic assumption that treatment, regardless of delivery method, will always have small to medium effects; that is, we have wrought as much efficacy as can be wrought given this disorder. Second, we could offer an optimistic assumption that combining future innovative technological applications with existing treatments will produce more robust outcomes for more patients. And last, we could assume that we have not yet discovered all the elements or aspects of addiction that render it robust. We view the future optimistically and anticipate that continued research exploring novel and different aspects of addiction and its treatment will reveal novel interventions and will demonstrate that we can obtain a large effect size. Whatever those novel treatments may consist of, we think that their use will be incorporated into technological approaches being developed today. These technologies can clearly extend the reach of our interventions, which will contribute to improving the lives of those suffering from problems related to addiction.

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Cultural Adaptation of Empirically-Validated Therapies for Treating Drug Dependence

61

Felipe González Castro and Manuel Barrera Jr.

Contents

Abstract

Efficacious drug abuse treatments (empirically validated treatments – EVTs) are those that have been designed by applying scientific theory and principles of effective drug abuse treatment. These EVTs are defined as efficacious when tested in randomized controlled trials that demonstrate that they "work" in promoting abstinence from drug use, in avoiding relapse, and in attaining targeted treatment outcomes. In principle, efficacious treatments should be implemented with fidelity in the delivery of the core elements necessary for

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effective treatment. By contrast, the need for local adaptations of these EVTs has emerged based on the considerable diversity in client needs that exists worldwide, given considerable variations in local cultural environments that exist within diverse communities worldwide. Issues of local adaptation are magnified when an EVT that is designed in one nation, such as the United States, is "exported" for use in another nation. The present chapter examines and analyzes issues in the local adaptation of EVTs to render them culturally relevant for treating members of local subcultural groups, while also maintaining the core elements that from scientific research must be delivered correctly to promote effective recovery from drug abuse and addiction. The Matrix Model is presented as an exemplar of an EVT that has been adapted for delivery within diverse communities worldwide. Also, stage models of common adaptation approaches and practices are examined. Finally, some practical approaches and recommendations are presented for conducting a local adaptation of an EVT within various nations or cultural communities.

61.1 Introduction

61.1.1 The Case for the Cultural Adaptation of Drug Abuse Treatments

Interest in the *adaptation* of model treatments – *evidence-based interventions* (EBIs) and *empirically validated therapies* (EVTs) – has increased in recent years (Carroll et al. 2011; Castro et al. 2010). This chapter examines issues, perspectives, and approaches in the cultural adaptation of original EBIs or EVTs, respectively, as examined within two research areas: (a) prevention interventions with adolescents and (b) drug abuse treatments with young adult and middle-aged clients.

Within the past decade, the strategy of adapting a validated model treatment, as opposed to its delivery with fidelity and thus without adjustment (Elliot and Mihalic 2004), has emerged as a significant and controversial approach. Some research investigators have argued that evidence-based interventions (EBIs) and empirically validated treatments (EVTs) (Carroll et al. 2011) should be disseminated widely to diverse client groups, and when implemented with high fidelity should work as designed, thus obviating any need for adaptation. By contrast, evidence from a study of school-based drug abuse prevention curricula (Ringwald et al. 2004) reveals that classroom teachers who administered manualized model prevention interventions frequently modified the original intervention because they saw significant limitations in the original model intervention. These teachers generally sought to modify the original EBI to make it more culturally relevant for their adolescent students. Similarly, among drug abuse counselors and therapists, fidelity in the delivery of original and validated EVTs has also been remarkably low (Carroll et al. 2011).

Regarding these efforts at local adaptation, teachers from schools populated by high percentages of racial/ethnic minority students were most active in making relevant adaptations. These adaptations focused on three major content areas: (a) adding content on preventing youth violence, (b) accommodating limited

English proficiency students, and (c) addressing issues relevant for racial and ethnic minority students (Ringwald et al. 2004). Although this example relates to substance use prevention interventions for adolescents within the United States, these adaptation issues parallel similar concerns in the adaptation of drug abuse treatments within the United States, as administered to underserved clients from major racial/ethnic minority populations – African Americans, Hispanics/Latinos, Asian Americans, and Native Americans.

61.1.2 Issues Involving Fidelity and Adaptation

Fidelity refers to the extent to which a treatment is delivered as originally developed and prescribed by the creators of that treatment and as implemented by the treatment's manualized procedures which have been validated within one or more randomized controlled trials (Flay et al. 2005). By contrast, the *adaptation* of a model treatment refers to modifications in one or more treatment components or activities with the aim of increasing treatment *relevance* and *effectiveness* for a specific subcultural group of clients (Castro et al. 2004). Such modifications often focus on treatment contents, activities, or forms of implementation as these neglect or conflict with the needs of a subcultural group of clients. Ideally, such adaptations will increase client engagement as well as the magnitude of treatment effects and thus the treatment's overall efficacy level.

In discussions on the relative merits of fidelity and adaptation, some research investigators have argued that original evidence-based treatment should *never* be adapted. They have argued that

> The Gold Standard is widespread adoption of model programs, implemented with fidelity, and sustained by routine funding sources within the community. The call for a negotiated balance and fidelity/adaptation has the potential for lowering this standard, encouraging and empowering local implementers to make questionable adaptations, and undermining the research community's commitment to fidelity. It could easily backfire and undermine public confidence and scientific claims that we have programs that work, if these programs prove effective when we take them to scale. (Elliot and Mihalic 2004, pp. 51–52)

In principle, each EBI and EVT should be broadly disseminated, thus making that treatment readily available to many communities and consumers. However, in practice, such broad-based dissemination and implementation has not been fully realized (Carroll et al. 2011). A general challenge involves the distinction between *adopting* an intervention or treatment "as is" and *adapting* that intervention with strategic adjustments to make it truly relevant and responsive to the needs of a local community and its consumers. Unfortunately, if a treatment lacks genuine *relevance* and *appeal* for local consumers, despite its efficacy rating, if local consumers dislike it and drop out, that treatment ultimately produces no benefits for these local consumers.

In the decade since these fidelity-adaptation controversies emerged, efforts to adapt model treatments have become "the rule rather than the exception" (Ringwald et al. 2004). One of several reasons for this may be that there exists no

"ideal" or entirely "universal" model treatment, a "one-size-fits-all," intervention that works well for everyone. Public health interventions that exhibit "universal" features typically consist of one-shot interventions, such as immunizations or seat belt use campaigns. By contrast, it becomes progressively more difficult to produce a "universal" and "one-size-fits-all" intervention, as an intervention increases in complexity, requiring several steps and a prolonged time frame to complete, e.g., an obesity reduction intervention. This difficulty also increases as a community exhibits greater diversity in its consumer populations and in the complexity of community needs and preferences.

The challenge of developing an entirely "universal" intervention increases exponentially when considering the expansive diversity of cultures that exist worldwide. For example, how can a single English-language drug abuse model treatment developed in the United States be implemented with complete fidelity, i.e., exactly as originally created and manualized within diverse countries such as Mexico, Spain, China, India, and Thailand? A more realistic scenario is that some form of *local adaptation* will be necessary, at very least involving a well-crafted linguistic translation, although it is likely that other cultural modifications will also be necessary.

61.1.2.1 Linguistic Translation of a Model Treatment

At the very least, *linguistic adaptations* are necessary when a model treatment originally developed in one language would be administered to people who speak a different language (Castro et al. 2004). By contrast, if a model treatment is grounded in scientifically established principles of human thought and behavior (Bandura 1986), these principles, as incorporated into an effective treatment, would be expected to generalize to a certain extent across many populations. In practice, the actual level of adaptation needed will depend on the extent of client-treatment non-fit as this treatment is administered initially within a new community setting or with a new cultural group.

61.1.2.2 Concerns over "Misadaptation"

Careful attention is needed to avoid making adaptation changes that actually lower the scientific standards of a model treatment, i.e., a misadaptation. "Misadaptation" occurs when making "a haphazard or inappropriate change in the prescribed procedures of a manualized model treatment" (Castro et al. 2010, p. 221). This can occur when program staff make arbitrary changes in a manualized model treatment, without a full understanding of that model treatment's core components and prescribed activities, as created by the developers of that model treatment. Clearly, misadaptation must be avoided, because it can erode treatment efficacy.

61.1.2.3 Issues from the Evidence-Based Movement

The *evidence-based movement* has emphasized the importance of creating and delivering empirically validated interventions and treatments (Norcross et al. 2006). Establishing that a treatment "works" is based on evidence from

clinical "best practices" and, better yet, from "empirical scientific research" regarding the treatment's efficacy or effectiveness (Flay et al. 2005), as established from one or more randomized controlled trials.

61.1.2.4 Concerns Expressed by Providers

Despite this scientific emphasis on evidence-based approaches, in the past, many treatment providers felt constrained by working with what they perceived to be overly prescriptive, restrictive, or culturally insensitive manualized treatments that they also judged to be unresponsive to the needs of racial/ethnic and other minority clients (Sue and Zane 2006). This dissatisfaction prompted ad hoc efforts by some service providers to modify or otherwise "informally adapt" a prescribed model treatment to address their clients' needs. As noted, such changes have been regarded by some treatment developers as entirely inappropriate and likely to erode the intervention's effectiveness (Elliott and Mihalic 2004).

61.1.2.5 Lessons Learned from the Clinical Trials Network

Regarding efficacious outcomes from drug abuse treatments, Carroll and collaborators summarized the lessons learned from 10 years of research from the NIDA Clinical Trials Network (Carroll et al. 2011). Regarding emergent issues that affect empirically validated therapies (EVTs) for drug abuse treatment, these investigators noted that (a) retention remains a major problem in substance abuse treatment and that promoting treatment retention is critical to treatment success; (b) EVTs are still not broadly implemented in practice and when implemented are often delivered with low fidelity; and (c) at the agency level, effort, support, and commitment are essential factors for adopting and sustaining an EVT given the costs of implementation, staff training, and supervision (Carroll et al. 2011). Given the importance of client retention, along with the problem of low utilization of EVTs, these issues should be addressed in the design of future EVTs to improve client retention by enhancing the treatment's cultural relevance as this can increase client engagement.

61.1.2.6 Cultural Considerations in Drug Abuse Treatment

In 1999, the National Institute on Drug Abuse published *NIDA's 13 Principles of Drug Addiction Treatment* (National Institute on Drug Abuse 1999). These principles are that (a) no single treatment is appropriate for all individuals; (b) treatment needs to be readily available, whereby delays in treatment availability can yield a loss of clients; (c) effective treatment attends to multiple needs, not just to drug use, and this includes attending to medical, psychological, social, vocational, legal, and other needs; (d) a continuous assessment and modification of a client's treatment plan is necessary to monitor changing needs and to respond accordingly; (e) remaining in treatment for an adequate period of time is crucial to treatment success – typically clients should remain in treatment for at least 3 months; (f) counseling and behavioral therapies are crucial components of treatment, as these can address treatment motivation, skill building, and problem solving; (g) medications are important components of treatment as they can reduce cravings, and this includes psychotropic medications for clients who need these;

(h) integrated treatment is needed for clients with psychiatric comorbidity; (i) medical detox is an important first step in treatment; and (j) treatment need not be voluntary to be effective, and engagement in such compulsory treatment is facilitated by familial, employment, legal, and other sanctions.

It is noteworthy that none of these 13 principles directly address issues of culture in the treatment of drug-dependent clients (Castro et al. 2007). A few years earlier, issues of culture and ethnicity were recognized as important for the complete and culturally sensitive treatment of many clients and primarily for those from racial/ethnic backgrounds (Ja and Aoki 1993; Terrell 1993). Terrell (1993) discussed several strategies for the design and implementation of efficacious alcohol and drug abuse treatments for racial/ethnic minority clients. These strategies include (a) assessing the client's immigration and acculturation experiences including their *acculturation stress*, as factors that can erode the protective effects of the client's traditional or native culture; (b) assessing a client's experiences with *discrimination*; and (c) developing *culturally responsive* treatment interventions (Terrell 1993). Today, the factors of race, ethnicity, gender, sexual orientation, and other cultural factors are considered important for a more complete treatment of diverse drug-dependent clients (Castro and Hernandez-Alarcon 2002; Castro et al. 2007).

Beyond these cultural issues, these 13 principles may be regarded as elements of drug abuse treatment that can operate as core treatment components. The multiplicity of these NIDA principles also underscores the complexities inherent in the delivery of a comprehensive drug abuse treatment. Such treatment also includes the need for ongoing monitoring of client progress and the need to make relevant adjustments that will optimize the treatment by tailoring it to the client's needs (Bernal et al. 2009).

61.2 Intervention Exemplar, Perspectives on Evidence, and International Considerations

61.2.1 Description of Approach

61.2.1.1 Exemplar of a Tested and Effective Drug Abuse Treatment Program

The Matrix Model is a manualized multicomponent model treatment. In its basic form, the Matrix Model consists of a 16-week program delivered in three sessions per week for a total of 48 sessions (Obert et al. 2000). The Matrix Model treatment includes (a) 12 family therapy sessions, (b) four social support group sessions, (c) four individual treatment sessions, and (d) a weekly breath alcohol testing and urine testing protocol. This treatment is nonjudgmental and nonconfrontational and includes positive reinforcement from therapists and peers for appropriate behavior change (Hillhouse et al. 2007; Rawson et al. 1995).

The Matrix Model was developed from the integration of empirically based interventions and "grassroots" clinical experiences (Rawson et. al. 1995).

This manualized treatment includes patient handouts and a patient workbook that introduce evidence-based recovery activities as developed from the integration of five theory-based treatment approaches: cognitive behavioral therapy (CBT), 12-step facilitation, motivational interviewing, contingency management, and family therapy (Obert et al. 2000). As developed from these five treatment approaches, the formal core components of the Matrix Model consist of (a) early recovery phase treatment activities, (b) relapse prevention, (c) social support groups, (d) family and conjoint sessions, (e) individual sessions, (f) urine testing, (g) relapse analysis, and (h) family education groups. The Matrix Model is guided by eight treatment principles which are conveyed to clients: (a) create explicit structure and expectations; (b) establish positive, collaborative relationship with the client; (c) teach information and cognitive behavioral concepts; (d) reinforce positive behavior change; (e) provide corrective feedback when necessary; (f) educate family regarding stimulant/drug abuse recovery; (g) introduce and encourage self-participation; and (h) use urinalysis to monitor drug use (Rawson et. al. 1995; J. Obert, 2 Apr 2013, personal communication).

61.2.1.2 Cultural Adaptation of the Matrix Modal

In principle, the cultural adaptation of the Matrix Model or any EVT begins by identifying problems in treatment implementation and also by identifying sources of client-treatment mismatches (non-fit) (Castro et al. 2004). This is followed by making strategic adaptations in treatment content, activities, or forms of delivery, as recommended by consumer feedback from key informants and stakeholders and as reviewed by a Cultural Advisory Committee. These adaptations would be accomplished (a) while seeking to maintain identified core treatment components (essential program activities); (b) increasing the cultural relevance of the treatment for local consumers (clients and subcultural groups); (c) increasing client motivation, engagement, and treatment involvement; (d) sustaining the efficacy of the treatment effect (i.e., maintaining the "effect size" on targeted outcomes); and (e) ideally increasing the treatment's "effect size" (Castro et al. 2010), that is, producing a greater and clinically significant magnitude of improvement on targeted outcome variables.

Moreover, effective cultural adaptation can ideally advance "beyond the black box," (Simpson 2004), meaning that these adaptations would introduce (a) a greater understanding of how cognitive behavioral theory or the treatment's logic model produces therapeutic improvements on targeted outcome variables and (b) greater knowledge of how cultural treatment factors improve the treatment's relevance for addressing client needs while also increasing the treatment's effect size.

Reducing Client-Treatment Mismatches

Conceptually, the greater the gap or *mismatch* between the core concepts and activities of the original model treatment, and the needs and preferences of a targeted group of clients, the greater the adaptive changes necessary to fit the needs of a targeted group of clients. For implementation in international venues, a relevant question is, "In what ways should an original EVT developed for

American drug-dependent clients be modified for application with specific groups of clients from another country?" In this regard, within the United States, certain "mainstream treatments" that were designed for middle-class White American clients were shown to be insensitive to the needs of many low-income African American and other racial/ethnic minority clients (Castro and Hernandez-Alarcon 2002; Sue and Zane 2006). This observation led to calls for *cultural sensitivity* in treatment development (Sue and Sue 1999) and also calls for greater *cultural competence* (Orlandi et al. 1992; Schwartz et al. 2010) among the counselors or therapists who would deliver these treatments. Such observations ultimately prompted the development of stage models for adapting such model treatments to better fit the needs of specific *subcultural groups* of clients (Barrera et al. 2011, 2013).

Need for Gender Sensitivity

As one historical example, in the past drug abuse treatments emerged primarily as treatments for drug-dependent male clients, inadvertently exhibiting insensitivity to the needs of many female drug-dependent clients (Greenfield et al. 2007). Such treatments did little to address certain critical issues that affect drug-dependent women, such as their victimization from domestic violence and abuse imposed by their partners, some of whom were also drug addicts. Thus, gender-sensitive programs were developed for application with drug-dependent women. Unfortunately, these treatments, when compared with conventional mixed-gender treatments, have *not* been shown via controlled randomized trials to be more effective in promoting recovery among drug-dependent women. Nonetheless, these gender-sensitive treatments have shown greater efficacy in addressing certain problems that are common among substance-abusing women (Greenfield et al. 2007).

61.2.2 Evidence to Support the Approach

61.2.2.1 Evidence Regarding the Effects of Core Components

In principle, intervention activities and procedures that constitute a treatment's "core components" are based on theory and on clinical procedures shown empirically to produce desired therapeutic effects. For example, and in principle, a treatment that utilizes principles from social cognitive theory (Bandura 1986) and cognitive behavioral procedures, e.g., contingency management, may exhibit near-universal effects on human behavior and thus would be generally applicable for treating clients from many parts of the world.

Given that the Matrix Model is based on social cognitive theory, as well as on principles from cognitive behavioral therapy (CBT) and family systems therapies, its major core components are (a) family sessions, (b) enhancing social supports, (c) individual treatment sessions, and (d) breathalyzer and urine testing. Thus, and in principle, within an adapted version of this model treatment, none of these core treatment components should be eliminated or modified. For example, the Matrix Model treatment might lose some of its treatment effectiveness if breathalyzer and urine testing were eliminated within a culturally adapted version of the original Matrix Model.

61.2.2.2 Evidence on the Need for Assessing Cultural Factors

A study in Belgium illustrates several core issues, as examined in an international setting, regarding the role of cultural factors in drug abuse treatment. That study conducted a qualitative analysis using in-depth interviews with drug treatment center staff and clients (Vandevelde et al. 2003). First, these investigators reported on problems emerging from the existing treatment system's client database, which did not collect data to distinguish the construct of "ethnicity" from "nationality." This omission led to a lack of information regarding ethnic issues, as these were conflated with very different issues that involve clients' nationality. From major ethnic themes involving ethnicity that emerged from these interviews, ethnic clients complained of a lack of cultural responsiveness in the drug abuse treatment that they received. Another theme involved cultural barriers in communication with the therapist. These barriers included problems in clients' ability to express themselves effectively in their own language, and this limitation became detrimental to progress in treatment. Other barriers included clients' perceptions that their own treatment needs conflicted with their therapist's Westernized world views. In summary, ethnic clients complained that the drug abuse treatment which they received lacked cultural relevance and responsiveness to their treatment needs.

Ironically, most of these clients and therapists recommended that developing a separate ethnic-specific treatment program would *not* be useful. Within the context of these complaints, these clients recommended that the conventional treatment program be retained yet also supplemented with attention to cultural factors and issues (Vandevelde et al. 2003). This outcome underscores the need to base drug abuse treatment on established scientific principles of recovery from addiction while also attending to issues of culture and local client needs. This case highlights the importance of integrating cultural sensitivity within an original drug treatment program, while also highlighting the importance of training culturally competent therapists. Such cultural issues can be addressed without replacing the treatment in its entirety, by adding one or more modules to the original treatment, to address specific cultural issues.

61.2.2.3 Evidence Regarding Engagement and Retention

As noted previously, in drug abuse treatment, several challenges exist regarding client engagement and retention (Carroll et al. 2011). One approach to increase treatment engagement and retention among youth and families is to reduce the total number of program sessions, e.g., from 12 to 8 sessions. However, some evidence indicates that a reduction in sessions can diminish program efficacy (Kumpfer et al. 2002), as clients may retain less essential knowledge and skills from this reduction in sessions.

Indices of Treatment Outcome

Based on research conducted with the Matrix Model, various indicators of client retention are as follows: (a) *engagement*, staying in treatment as assessed at the 2-week and 1-month observations; (b) *retention*, staying in treatment as measured by the number of weeks remaining in treatment, with a maximum of 16 weeks, and

also as measured by staying in treatment for 90 days or more versus less than 90 days; (c) *abstinence*, as indicated by the average number of drug-free urinalysis tests collected during treatment and the occurrence of three consecutive drug-free urine analyses during treatment; and (d) *completion*, the completion of the 16-week Matrix Model treatment with no more than two consecutive missed weeks of treatment versus non-completion of this 16-week program (Hillhouse et. al. 2007).

These indices of client participation are likely correlated, although each provides slightly different indicators of treatment outcomes. As one example, from the Matrix Model, significant predictors of abstinence following treatment from methamphetamine abuse were female gender, a high frequency of methamphetamine use at treatment entry (15 days or more of use), and the client's route of drug administration (e.g., injection drug use) (Hillhouse et al. 2007). Also, criteria on route of administration indicated that the more severe form of self-administration, e.g., injection versus snorting, was associated with lower rates of abstinence. Regarding gender differences, the reason why women exhibited greater difficulties in maintaining abstinence relative to men was unclear (Hillhouse et al. 2007).

61.2.3 International Considerations

61.2.3.1 General Considerations in Dissemination and Implementation

As an EVT (Shoptaw et al. 1994), a major Matrix Model treatment goal involves its broad dissemination to enhance the availability of EVT to help drug-dependent clients. The successful dissemination and implementation of evidence-based interventions (EBIs) and of empirically validated therapies (EVTs) offers great potential for increasing public health and well-being (Spoth et al. 2013). This pursuit, identified as "type 2 translation research," involves generating scientific evidence on best approaches for (a) building community and agency infrastructures to deliver EVTs and EBIs, (b) creating practitioner-scientist partnerships, and (c) establishing effective implementation procedures for adopting, implementing, and sustaining EBIs and EVTs within diverse community settings (Spoth et al. 2013).

As an exemplar of this pursuit, the Matrix Model has been translated into nine languages and disseminated to over 6,000 therapists or counselors in the United States and internationally, as taught by 320 key supervisors. These supervisors have conducted Matrix Model training in 21 countries and in all 50 of states of the United States, resulting in staff training conducted in over 2,500 treatment agencies (J. Obert, 2 Apr 2013, personal communication).

Based on challenges from Matrix Model dissemination efforts as conducted in Thailand, Mexico, and in other countries worldwide, the developers of the Matrix Model have drawn several observations to guide future dissemination and implementation efforts. First, despite the availability of a published Matrix Model treatment manual, this treatment cannot be delivered effectively from this manual alone; formal training of Matrix Model implementers is necessary. Second, at the organizational and community levels, agency and civic leaders must understand fundamental aspects of drug abuse treatment to provide appropriate support that

ensures correct treatment implementation and avoids administrative decisions that conflict with or that undermine Matrix Model principles and activities (J. Obert, 2 Apr 2013, personal communication). Third, dissemination efforts must be guided by a clear dissemination plan that is monitored for quality and professionalism in its implementation. As a result of prior difficulties encountered in initial dissemination efforts, the developers of the Matrix Model also designed a certification program to ensure quality in training of Matrix Model therapists and counselors. The aim is to implement this treatment with requisite fidelity and with treatment insights regarding fidelity of implementation and/or adaptation planning when encountering problems in the implementation of the Matrix Model (J. Obert, 2 Apr 2013, personal communication).

61.2.3.2 General Considerations in International Adaptations

The world is a diverse place in which cultural diversity is expressed in a multiplicity of spoken languages, variations in literacy levels, diversity of religious and cultural systems of beliefs, and a multiplicity of sociocultural attitudes, values, and norms as exhibited across nations and even within nation. Within this context, worldwide there exists a dynamic tension between the sociocultural forces of *modernization* and quests for change and *traditionalism* and quests for the preservation of tradition and a resistance to change (Shiraev and Levy 2010). Factors that promote modernism, such as international globalization, emphasize growth and standardization and operate as forces that tend to homogenize cultural practices. By contrast, factors that promote traditionalism and its indigenous perspectives (Ramirez 1999) tend to diversify whole populations into distinct subcultural groups, emphasizing the retention of unique cultural and local identities and lifeways. These broad cultural influences provide a systemic context against which to consider the cultural adaptation of EBIs and EVTs.

61.2.3.3 Stage Models of Adaptation and Applications Across Cultures

Within the past decade, several stage models have been developed to guide the cultural adaptation of prevention and treatment interventions (Barrera and Castro 2006; Domenech Rodrıguez and Wieling 2004; Kumpfer et al. 2008; McKleroy et al. 2006; Wingood and DiClemente 2008). Several of those models were developed for the adaptation of treatments developed initially for majority middle-class populations within the USA, as these original EBIs or EBTs could be modified for greater relevance as delivered to member of the major US subcultural groups, i.e., African Americans, Hispanics/Latinos, Asian Americans, and Native Americans. However, with few exceptions (Kumpfer et al. 2008; Wingood and DiClemente 2008), cultural adaptation models have *not* been developed for international applications in which EVTs and EBIs created in one country have been adapted culturally for use in another country.

Segmentation: Beyond "Country" as the Unit of Analysis

One important way to frame the approach to cultural adaptation is to think beyond "the country" as the units of analysis that are smaller and more culturally

homogeneous that the 'nation' as a whole. A more useful approach is to consider adaptation for a *local community* or *region* of a country, given the remarkable within-country heterogeneity that exists within most countries worldwide. In other words, sensibly adapting an original EVT "for Mexico" requires a more refined approach to adaptation, one that considers a *smaller unit of analysis* rather than an entire nation. Adaptation to a local region or to a local community is critically important. This more *microlevel* approach advances beyond an "ethnic gloss" (Trimble 1995) that occurs under a more *macro-level* of analysis, i.e., the nation, given that a macro approach often glosses over important within-country variations.

For example, in considering the cultural adaptation of the Matrix Model for use "in the country of Mexico," besides a translation from English to Spanish, this adaptation would also require variations for its use within large urban and lower- and middle-class environments, such as within Mexico City and Guadalajara. By contrast, a second modified and adapted version may be needed for use with residents from rural and indigenous communities, such as with residents from the Mexican states of Chiapas and Yucatan. For example, within indigenous Mexico, some local residents have very low literacy levels and may not communicate well in Spanish, with some not speaking Spanish as their preferred language. Thus, a linguistic adaptation of the Matrix Model to Spanish could render this adapted version only partially relevant when administered with an indigenous subcultural group from the region of Chiapas, Mexico. And such a linguistic adaptation alone would not address long-standing cultural traditions, thus also highlighting the need for a local or regional cultural adaptation. Some rural indigenous males from this region of Mexico may also have culturally based *macho* gender role norms and expectations that confer them with considerable male authority and privilege over their family and within their community. Such traditions and cultural practices must be addressed if this treatment is to engage such clients in culturally relevant activities and operate effectively with the male residents of this local community.

Approaches to International Adaptation

A recent article has presented an international model of intervention adaptations, an approach titled *Planned Intervention Adaptation* (PIA) (Sundell et al. 2013). The authors described PIA as a synthesis of several models that outline stages or conceptual frameworks for systematically adapting interventions for applications in new cultural contexts (Sundell et al. 2013). PIA consists of two broad phases that were inspired particularly by Resnicow and colleagues, who distinguished between the concepts of "deep structure" elements of an intervention from "surface structure" elements (Resnicow et al. 2000).

In reality, PIA is not fundamentally different than other cultural adaptation stage models (see Barrera et al. 2013). However, it does distinguish itself from others in the detail of its recommendations. For example, PIA specifies a time period for the initial adaptation stages and a sampling strategy for formative studies. Phase 1 of PIA consists roughly of a 1.5–2-year period when intervention developers and stakeholders (agency staff, potential consumers) agree to collaborate on five

preliminary steps that are summarized in a table and detailed in text (e.g., language translations, tests of translated materials, focus group checks on the cultural appropriateness of intervention materials and activities). These preliminary steps help to shape the adapted intervention.

In phase 2 of PIA, the authors recommend conducting a three-arm effectiveness study which would consist of (a) a minimally adapted intervention (solely surface structure changes such as language translation), (b) a fully adapted intervention (both surface and deep structure changes), and (c) a control condition. However, even for this recommendation, given the complexities in conducting *conceptually equivalent* linguistic translations, a linguistic translation itself may actually involve more than just surface changes. The PIA also recommended the inclusion of appropriate measures and data analytic procedures to identify possible mediators and moderators of intervention effects (Iacobucci 2008; MacKinnon 2008). Unfortunately, based on Sundell et al. (2013) article, it is not certain that the PIA framework actually has been used in the international adaptation of an original EVT intervention.

Undoubtedly, the best examples of international adaptations involve studies of the Strengthening Families Program (SFP), a family skills intervention for the prevention of youth substance abuse (Kumpfer et al. 2008). SFP was initially developed and tested in the United States and subsequently has been adapted for applications in Australia, Canada, Central America, Europe, South America, and Southeast Asia. The results of that work have been summarized with the following statement (Kumpfer et al. 2012, p. 176):

> Replications of SFP in non-experimental and quasi-experimental studies in about 17 countries and randomized control trials (RCTs) in nine countries (United States, Canada, Australia, UK, Sweden, Netherlands, Spain, Italy, and Thailand) with different cultural groups by independent evaluators have found SFP to be an effective program in reducing multiple risk factors for later alcohol and drug abuse, mental health problems and delinquency by increasing family strengths, children's social competencies and improving parent's parenting skills.

Kumpfer et al. (2012) detailed 10 steps that should be followed in creating an international adaptation of SFP and perhaps for other evidence-based programs (also see Kumpfer et al. 2008). Table 61.1 summarizes these ten steps. In Kumpfer et al. (2008), these steps were illustrated with examples from their extensive experience in many countries. This "must-read" article is filled with general guidance and best practices for those who are planning international adaptations of evidence-based interventions.

61.2.3.4 Conducting a Streamlined Cultural Adaptation: A Five-Stage Model

We recognize that many drug abuse treatment programs in the United States and also in various communities worldwide are delivered within medical centers and in a variety of community-based agencies, large and small. These professional settings often do not have the requisite research infrastructure (the program evaluation or

Table 61.1 Two systematic approaches to cultural adaptation

Step	Action (from Kumpfer et al. 2012)	Stage	Action
1	*Needs assessment* – collect needs assessment information from new or existing data to determine major family risk and protective factors for child developmental problems	1	*Information gathering* – review of the current drug treatment literature and a screening of client-treatment mismatches
2	*Literature review* – collect information from research literature or websites on appropriate family skills. Select the best program for age, ethnicity, and risk level of families (e.g., universal, selective, or indicated prevention approaches)		
3	*Cultural adaptation team* – create a cultural adaptation team including family members and the original program developer	2	*Preliminary adaptation design* – propose adapted modifications of specific mismatched content or activities for the original model treatment
4	*Linguistic translation* – translate into local language and do minor cultural adaptations		
5	*Initial implementation* – implement "as is" with minimal adaptation at first	3	*Preliminary adaptation test* – test this pilot adaptation to assess how well it works with clients from the targeted subcultural client group
6	*Implementation of initial changes* – have implementers from local culture make gradual changes based on what works (culturally appropriate language, stories, songs)		
7	*Ongoing cultural adaptations* – continuously make additional cultural adaptations and add to curriculum with the program developer's approval	4	*Adaptation refinement* – using client feedback from the prior stage, make adjustments on revisions to refine the emerging adapted model treatment
8	*Ongoing evaluation* – continuously conduct pre-and posttest evaluations on each family group to measure if the local cultural adaptations are making the program better or worse	5	*Cultural adaptation test* – as viable, conduct a small-scale or ideally a large-scale randomized controlled trial to formally assess the efficacy of the adapted model treatment, as compared with the original model treatment, and ideally also against a treatment-as-usual (TAU) control group
9	*Add or drop adaptations* – make adjustments to add or drop new cultural adaptations		
10	*Dissemination to similar groups* – disseminate the culturally adapted version to similar cultural groups if effective		

research staff, the funding and time, and other research or evaluation resources) to conduct a formalized and months-long randomized controlled clinical trial to test the efficacy of an EVT adaptation as described by Sundell and colleagues and by Kumpfer and colleagues.

61.2.3.5 A Practical Approach to the Cross-Cultural Adaptation of a Treatment Program

How then might a treatment center or community-based agency conduct a cost-effective, culturally responsive, and scientifically defensible cultural adaptation of an original EVT? Within such an abbreviated cultural adaptation effort, to avoid engaging in misadaptation, we encourage rigor in the application of scientific and community-based participatory research procedures (CBPR) (Minkler and Wallerstein 2003; Minkler et al. 2008). This abbreviated approach would aim to achieve, and perhaps enhance, certain targeted treatment outcomes: (a) treatment engagement, (b) retention in treatment, (c) abstinence from drug use, and (d) program completion (Hillhouse et al. 2007). And as noted, another goal is to avoid introducing iatrogenic effects as consequences of misadaptation.

61.2.3.6 General Strategy and Procedures for a Streamlined Intervention Adaptation

An initial assessment step in the cultural adaptation of an original EVT is to establish a Cultural Advisory Committee to identify and address cultural and other forms of local problems in treatment implementation and in client-treatment mismatches. Such culturally incongruous content or activities are characterized as elements of treatment that are found to be confusing, objectionable, or culturally offensive to members of a targeted subcultural client group. Under a community-based participatory research approach (CBPR), these forms of mismatch are identified by conducting *focus groups, key informant interviews,* and interviews with *stakeholders* and with clients who represent other clients who would be recipients of this treatment (Parasi et al. 2011). Also to be included are interviews with treatment staff and administrators who would deliver this treatment. The identification and assessment of cultural mismatches would reveal significant problems in the implementation of the original EVT, as well as approaches for correcting them. If not identified and addressed initially, such sources of cultural non-fit can alienate members of a targeted client group and induce them to drop out of treatment.

Castro et al. (2004) outlined three major dimensions of model treatment adaptation. These three major dimensions are as follows: (a) *cognitive information processing* characteristics, such as language and age/developmental or literacy levels; (b) *affective-motivational* characteristics, including gender, racial/ethnic identity and background, religious background, and socioeconomic status, as these factors can influence clients' comfort in accepting the EVT's messages and activities; and (c) *environmental* characteristics, including ecological aspects of the client's local community:

1. *Cognitive informational adaptation* involves changing program contents or activities that clients are unable to understand. In international adaptations, this would involve a linguistic translation to achieve equivalence in meaning (conceptual equivalence), and not in a word-for-word translation (Camfield and Ruta 2007; Geisinger 1994; Gonzalez et al. 1995).

This should also take into account the literacy level of members of the targeted subcultural group.

2. *Affective-motivational adaptation* involves modifications of program content or activities that can induce *cultural conflict* or that *prompt reactance* (behavioral resistance). An example might be a Westernized cultural approach that requires male clients to publically disclose their drug dependence or to discuss sexual issues in the presence of certain family members. Without understanding its possible cultural implications, that practice might be perceived by traditional culture males as culturally inappropriate, whereby they may feel stigmatized and resist participating in this otherwise important treatment activity. Conversely, as a culturally modest adaptation, eliminating a discussion of stimulant use as a trigger for sexual arousal and activity can undermine drug treatment, given the association between stimulant use and sexual activity, as this can trigger a relapse episode (J. Obert, 2 Apr 2013, personal communication). Thus, a discussion of benefits and liabilities from such adaptations is critical for making sound adaptation decisions that are both culturally sensitive and that also adhere to scientific principles of effective drug abuse treatment.
3. *Environmental adaptation* involves therapeutic changes in a client's family system, in the client's home neighborhood, and within the treatment agency, thus modifying local environment conditions to aid in the client's recovery. In this domain, two basic forms of adaptation consist of (a) modifying *program content* which relates to the environment and (b) modifying the *form of program delivery*. Modification of content would include shallow or deep structure changes in that content. Changes in form of delivery would involve presenting the same treatment content, although delivered with changes in (a) *characteristics of delivery personnel*, lay health workers rather than health educators; (b) *channel of delivery*, Internet delivery rather than a group session; or (c) *location of delivery*, improving access by delivering the program within a church setting rather than within a drug treatment center.

61.2.3.7 Five Basic Stages in a Local or Cultural Adaptation

In a version that parallels Kumpfer's ten-step approach to cultural adaptations, the cultural or local adaptation of an original drug abuse model treatment (an empirically validated therapy – an EVT) can be conducted via a basic five-stage process (Barrera et al. 2013). Ideally, this five-stage process is conducted formally under a randomized controlled trial. In the absence of that option, four of these five stages can be conducted using a community-based participatory research (CBPR) approach as overseen by a well-informed Cultural Adaptation Committee (CAC). Accordingly, this adaptation effort as conducted by a drug treatment agency would be conducted (a) with the aid and oversight of a Cultural Adaptation Committee and (b) by using CBPR procedures to facilitate input from key informants and stakeholders and a review of consumer feedback to attain culturally sensitive and also scientifically informed decisions on appropriate adaptations. The CBPR approach is a bidirectional approach that consists of a collective dialogue and group decision in adapting an original EVT protocol (Donovan et al. 2011).

Table 61.1 presents these five stages as described by Barrera and colleagues (2013). Based in this framework and process, these five stages are:

1. **Information gathering** – Review relevant drug treatment literature as background to identify implementation problems and sources of client-treatment mismatches, as linked to the three major dimensions of cultural adaptation assessment, along with proposed adaptive changes that consider (a) participant characteristics, (b) program delivery staff, and (c) administrative/community factors (see Castro et al. 2004).
2. **Preliminary adaptation design** – Integrate recommendations from the Cultural Adaptation Committee which is staffed by (a) various stakeholders, (b) community experts, (c) developers of the model treatment, and (d) former clients or representatives from the drug treatment program (treatment insiders) and, if needed, other important representatives from the local community or treatment center. Core intervention components would be preserved, unless there exists convincing evidence that one of these core components is detrimental to the well-being of clients from the targeted constituency.
3. **Preliminary adaptation tests** – Design and pilot test a preliminary adapted version of the original EVT to assess (a) the elimination of prior implementation difficulties, (b) the emergence of problems with content or activities, (c) client satisfaction with treatment elements, and (d) suggestions for improvement.
4. **Adaptation refinement** – Revise the adapted intervention. Then, if viable as a more formal adaptation activity, proceed to stage 5.
5. **The cultural adaptation trial –** Formally determine the efficacy of this adapted version by comparing it to a treatment-as-usual (TAU) control group and ideally to the original EVT. This adapted EVT's efficacy can be assessed as it influences identified psychological and health outcome variables, as well as the assessment of engagement indicators (e.g., client involvement, client attendance, completion of the treatment). Although seldom evaluated, within the cultural adaptation trial stage, intervention evaluators or research investigators should aim to assess the effects of the adapted EVT on specified mediators and moderators (Iacobucci 2008; MacKinnon 2008). For example, if a culturally adapted EVT adds a cultural pride component, a mediation analyses could determine whether the intervention was successful in enhancing cultural pride and then if this cultural pride enhancement exerts an effect in reducing drug use or in avoiding relapse. Similarly, moderator analyses could be conducted to determine if the culturally adapted EVT was differentially effective: (a) for men versus for women, (b) for clients high versus low in levels of acculturation, (c) among immigrants versus natives, or (d) for any other potential moderators of intervention efficacy (Barrera et al. 2012).

In addition, the adaptation team could utilize a rigorous mixed methods research design (Creswell et al. 2011), one that includes in-depth interviews with participants and interventionists, to conduct a more in-depth assessment of treatment outcomes and of the process involved in the implementation of this adapted EVT (Castro et al. 2014). This approach would allow a deep structure analysis of client and therapist commentaries on factors that (a) may operate as core treatment

components, (b) may operate as sources of problems within treatment, and (c) factors that worked very well and should be kept along with (d) client feedback for enhancing the content or delivery of treatment modes to aid in treatment revisions as incorporated into a future adaptation of this once-adapted EVT.

61.2.3.8 Some Observations/Recommendations for Adaptation of Drug Abuse EVTs

From this analysis of the cultural adaptation of EVTs and EBIs and their international considerations, we offer a few observations and recommendations.

Enhancing Client Engagement

Sufficient client engagement in treatment to promote client retention and treatment completion remains a pervasive problem that affects treatment efficacy and the benefits that can be derived from that treatment (Carroll et al. 2011). It is thus essential that newly developed, adapted, or refined EVTs and EBIs increase their capacity for client engagement.

Treatment Relevance and Fit

A treatment that is not designed with the needs of a specific subcultural group may exhibit insensitivity to that group's needs and preferences. Given that early drug abuse treatments emerged with a distinct male focus, it exhibited insensitivity to the needs of many drug-dependent women. That is, it lacked relevance and fit for many women, until it was recognized that the treatment of drug dependence also needed to consider the unique needs of women.

Importance of Cultural Factors

Recent studies have highlighted the importance of considering various cultural factors, such as gender, racial or ethnic identity, sexual orientation, and levels of acculturation as influences on recovery from drug dependence. Drug abuse treatments can be enhanced by incorporating a cultural sensitivity to these and other cultural factors to promote full recovery among diverse drug-dependent clients and to avoid relapse (Castro et al. 2007).

Increasing Cultural Relevance Without Reconstructing a Treatment

Increasing an existing EVTs cultural relevance need not involve a complete reconstruction of an existing EVT. Adding a relevant treatment module or culturally relevant content and activities may be sufficient to enhance treatment relevance and client-treatment fit.

Cultural Adaptation as a Systematic and Team Effort

The effective adaptation of an EBI or an EVT consists of a planned and systematic team effort, one that involves a scientist-provider partnership between the developers of the treatment and other stakeholders (Donovan et al. 2011). Organized agency structures are also needed and should be developed to conduct the most

rigorous treatment adaptation possible within the local community and also to sustain the delivery of that treatment with the requisite fidelity needed to produce efficacious treatment results.

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Section V

Social Therapies and Treatment Settings

Gregory Bunt and Mahmood Nazar Mohamed

Social Therapies and Treatment Settings: An Introduction

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Gregory Bunt and Mahmood Nazar Mohamed

Despite the advances in the neuroscience of addictive disorders, there is no indication that a biological cure for the disorder of addiction is at hand. To the contrary, the overwhelming consensus of experts in addictive disorders is that the disease of addiction is a bio-psycho-social-spiritual phenomenon. The recent definition of an addiction developed by a task force of the American Society of Addiction Medicine and adopted by the International Society of Addiction Medicine underscores this point.[1]

Over the decades since the original establishment of Alcoholics Anonymous and the introduction of opioid maintenance therapy, a diverse group of socially grounded treatment settings have been developed worldwide. Most have been framed so as to adapt to respective national settings where they operate. Furthermore, the cost-effectiveness of many of the social therapies described provides practical public access to treatment for addictive disorders; and this is essential for effective local, regional, and national responses to the addiction crisis.

In this section of the textbook, we consider approaches which can be grouped into several key areas. There were peer-led treatments largely falling into two domains: (1) those which are peer led but not formally imbedded in structured programs or funded by government agencies or subject to regulations and (2) those which are institutionally based and regulated by governments such as therapeutic communities.

[1]The Definition of Addiction ASAM Public Policy Statement Adoption Date: April 12, 2011

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Therapeutic communities emerging in the 1960s with Daytop Village, Phoenix House, Odyssey House, and Samaritan Village are multisite programs with Daytop in fact expanding internationally. These programs are based on the premise that transformation of pathological character traits can lead to a resolution of drug-seeking behavior. The noninstitutional peer-based programs exemplified by Alcoholics Anonymous and Narcotics Anonymous, both emerging from centers in the United States altogether with over 150,000 peer-led groups worldwide, are premised on peer support infused with spiritual renewal. Densingi in Japan is also peer led but does not emphasize spirituality to the same degree.

Two chapters related to service delivery illustrate the complexity of various treatment networks constituted of diverse approaches. The policy initiatives and technology-based approaches are described with an emphasis on specific examples of innovative service delivery. Additionally, strategies for drug abuse prevention in the workplace provide another example of the introduction of treatment methods into a broader social context.

Inevitably, the illness of addiction impacts on both the criminal justice system and the acute medical emergency services, and in recent years, there has been considerable progress in moving addiction treatment forward into settings outside of those directed specifically at treatment, i.e., prison settings; forensic applications as Drug Courts, or alternatives to incarceration; or legal civil sanctions. Additionally considerable sophistication has been introduced into the Emergency Medical Services for addicted patients.

We can learn a great deal indeed from examining the diversity of clinical approaches in differing cultural, regional, and national settings. Whether in the United States, Japan, Malaysia, Iceland, the United Arab Emirates, Vietnam, Lebanon, or any other nation delivering addiction treatment services worldwide, the diversity of options and opportunities for developing and advancing addiction services remains a vital challenge for the professionally trained addiction physician today.

Altogether, these diverse but carefully framed aspects of social therapies illustrate the many ways in which social support and structure, both in formal treatment settings and outside of them, have emerged since the twentieth century. The skill, wisdom, and knowledge with which addiction physicians apply these principles of social therapies and treatment settings for addictive disorders will have an enormous impact on the future of our field.

Therapeutic Communities for Addictions: Essential Elements, Cultural, and Current Issues

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Abstract

The therapeutic community (TC) is a major treatment modality serving a wide spectrum of substance abuse clients worldwide. The weight of the research evidence developed over some 40 years demonstrates that the TC is an effective and cost-effective treatment particularly for substance abusers with serious social and psychological problems in addition to their drug abuse. This chapter provides an overview of the essential elements of the TC approach: its perspective, method, program model, and adaptation for special populations, settings, and different cultures.

TCs have been successfully modified for special populations of substance users including those with co-occurring disorders, adolescents, women with children, criminal justice clients in prisons, and community-based settings. TC programs have been implemented in Europe, Asia, Africa, Latin America, and the Middle East. And, despite ethnic, social-political, and religious differences, TCs have retained their essential elements and effectiveness across a variety of cultures.

Its evolution over some 50 years has surfaced key issues that challenge the TC to maintain the integrity of its unique social psychological approach – community as method. Several of these are briefly highlighted including funding, workforce, research, treatment fidelity, and the diversity of TC programs. In the current context, the TC is compelled to reassert its place and mission in human services – that of promoting recovery and right living.

63.1 Introduction

Drug-free residential programs for substance abuse appeared a decade later than did therapeutic communities (TCs) in psychiatric hospitals pioneered by Maxwell Jones and others in the United Kingdom. The term therapeutic community evolved in these hospital settings, although the two models arose independently.

The TC for substance abuse emerged in the late 1950s as a self-help alternative to existing conventional treatments. The originators were recovering alcoholic and drug-addicted individuals (Yablonsky 1965, 1989). Although its modern antecedents can be traced to Alcoholics Anonymous and Synanon, contemporary TCs for addictions are sophisticated human services institutions. Today, the label therapeutic community is generic, describing a variety of short- and long-term residential and nonresidential programs that serve a wide spectrum of substance

abuse clients. Although the TC approach has been adapted for different populations and settings, it is the perspective and method of the traditional long-term residential prototype for adult substance abusers that has documented effectiveness in rehabilitating substance-abusing individuals.

63.2 Essential Elements

63.2.1 The TC Perspective

The TC perspective or theory shapes its program model and its unique approach, community as method. The perspective consists of four interrelated views of the substance use disorder, the individual, recovery process, and healthy living.

63.2.1.1 View of Disorder

Drug abuse is viewed as a disorder of the whole person, affecting some or all areas of functioning. Cognitive and behavioral problems are often present, as are mood disturbances. Thinking may be unrealistic or disorganized; values may be confused, nonexistent, or antisocial. Frequently, the patient exhibits deficits in verbal, reading, writing, or marketable skills. Moral or even spiritual issues, whether expressed in existential or psychological terms, are apparent. Thus, the TC perspective considers the problem to be the individual, not the drug, and addiction is a symptom, not the essence of the disorder.

63.2.1.2 View of the Person

In TCs, individuals are distinguished along dimensions of psychological dysfunction and social deficits rather than according to drug use patterns. Regardless of differences in social background, drug preference, or psychological problems, most individuals admitted to TCs share clinical characteristics (Table 63.1). Whether they are antecedent or consequent to serious involvement with drugs, these characteristics are commonly observed to correlate with chemical dependency. More important, in TCs, a positive change in these characteristics is considered to be essential for stable recovery.

63.2.1.3 View of Recovery

In the TC perspective recovery extends beyond drug freedom, involving a change in lifestyle and in personal identity. The primary psychological goal is to change the negative patterns of behavior, thinking, and feeling that predispose the individual to drug use; the main social goal is to develop the skills, attitudes, and values of a responsible drug-free lifestyle.

In many TC residents, vocational and educational problems are marked; middle-class, mainstream values are either missing or not sought. Usually these residents emerge from a socially disadvantaged sector. Their recovery in the TC is better termed *habilitation*, the development of a socially productive, conventional

Table 63.1 Typical behavioral, cognitive, and emotional characteristics of substance abusers in therapeutic communities

Low tolerance for all forms of discomfort and delay of gratification
Problems with authority
Inability to manage feelings (particularly hostility/anger, guilt, and anxiety)
Poor impulse control (particularly sexual or aggressive impulses)
Poor judgment and reality testing concerning consequences of actions
Unrealistic self-appraisal regarding discrepancies between personal resources and aspirations
Prominence of lying, manipulation, and deception as coping behaviors
Personal and social irresponsibility (e.g., inconsistency or failures in meeting obligations)
Marked deficits in learning and in marketable and communication skills

lifestyle for the first time. Among individuals from more advantaged backgrounds, the term *rehabilitation* is more suitable, which emphasizes a return to a lifestyle previously lived, known, and perhaps rejected.

63.2.1.4 View of Right Living

TCs adhere to certain precepts and values that constitute a view of healthy personal and social living that guide and reinforce recovery. For example, community sanctions address antisocial behaviors and attitudes; the negative values of the street, jails, or negative peers; and irresponsible or exploitative sexual conduct. Positive values are emphasized as being essential to social learning and personal growth. These values include truth and honesty (in word and deed), a work ethic, self-reliance, earned rewards and achievement, personal accountability, responsible concern (being one's brother's or sister's keeper), social manners, and community involvement. The precepts of right living are constantly reinforced in various formal and informal ways (e.g., signs, seminars, in groups and community meetings).

63.2.2 The TC Approach: Community as Method

The TC approach can be summarized in the phrase "community as method" (De Leon 1997, 2000). A parallel concept – "community as doctor" – in the psychiatric or democratic TC was first coined by Rapoport (1960). Theoretical writings offer a definition of "community as method" as follows: the *purposive* use of the community to teach individuals to *use* the community to change themselves. The fundamental assumption underlying the TC approach is that individuals obtain maximum therapeutic and educational impact when they engage in and learn to use all of the activities, elements of the community as the tools for self-change. Thus, community as method means that the community itself provides a *context* of relationships and activities for social learning. Its membership establishes the *expectations* or standards of participation in community activities; it continually *assesses* how individuals are meeting these expectations and *responds* to them with strategies that promote continued participation.

63.2.3 TC Program Model

The key components of the program model are its social organization (structure), peer and staff roles, groups and individual counseling, community enhancement meetings, community management elements, and program stages. Each component reflects an understanding of the TC perspective and each is used to transmit community teachings, promote affiliation, and self-change.

63.2.3.1 Social Organization

The TC social organization is stratified with relatively few staff of the TC at the top complemented by resident peers at junior, intermediate, and senior levels. This peer level-to-community structure strengthens the patient's identification with a perceived ordered network of individuals. More important, it arranges relationships of mutual responsibility at various levels in the program.

The daily operation of the community itself is the task of the residents, who work together under staff supervision. The broad range of resident job assignments illustrates the extent of the self-help process. Residents perform all house services (e.g., cooking, cleaning, kitchen service, minor repair), serve as apprentices, run all departments, and conduct house meetings, certain seminars, and peer encounter groups.

The TC is managed by the staff, who monitor and evaluate patient status, supervise resident groups, assign and supervise resident jobs, and oversee house operations. The staff members conduct therapeutic groups (other than peer encounter groups), provide individual counseling, and organize social and recreational projects. They make decisions about resident status, e.g., discipline, promotion, transfers, discharges, furloughs, and treatment planning.

63.2.3.2 Peers as Role Models

Peers, serving as role models, and staff members, serving as role models and rational authorities, are the primary mediators of the recovery process. TC members who demonstrate the expected behaviors and reflect the values and teachings of the community are viewed as role models. TCs require multiple resident and staff role models in order to maintain the integrity of the community and ensure the spread of social learning effects.

63.2.3.3 Staff Members as Rational Authorities

Staff members foster the self-help learning process through performance of their managerial and clinical functions described above but also as role models and rational authorities. TC residents often have had difficulties with authorities who have not been trusted or who have been perceived as guides and teachers. Therefore, residents need a positive experience with an authority figure who is viewed as credible, supportive, corrective, and protective so that they may gain authority over themselves (personal autonomy). As rational authorities, staff members provide the reasons for their decisions and explain the meaning of consequences particularly in terms of recovery and personal growth.

63.2.3.4 Therapeutic Educational Activities (Groups and Individual Counseling)

Various forms of group process and individual counseling provide residents with opportunities to express feelings and resolve personal and social issues. They increase communication and interpersonal skills, bring about examination and confrontation of behavior and attitudes, and offer instruction in alternative modes of behavior. The main forms of group activity in the TC are peer-led encounter groups, staff-led therapy, and tutorial groups. Other groups that convene regularly or held as needed supplement the main groups. These vary in focus, format, and composition and include gender, ethnic, age-specific, or health theme groups. Additionally, cognitive-behavioral tutorials using manualized curricula are employed for targeted areas such as relapse prevention, criminal thinking, trauma and PTSD, etc.

One-to-one counseling balances the needs of the individual with those of the community. Peer exchange is ongoing and is the most consistent form of informal counseling in TCs. Staff counseling sessions may be regularly scheduled or conducted as needed. The focus of staff counseling is to address issues that may impede progress and to facilitate the patient's adjustment to and constructive use of the peer community. Counseling is also employed for the purpose of developing an individualized treatment plan.

63.2.3.5 Community Enhancement Activities (Meetings)

Community enhancement activities are the facility-wide meetings that convene daily. These include the morning meeting, the seminar, the house (evening) meeting, and a general meeting. Some of these are held almost daily while others are called when needed. These gatherings are necessary for building the spirit of community to which members are expected to participate actively. Though different in format, all meetings have the common objective of facilitating the individual's assimilation into the community. The purpose of the morning meeting is to instill a positive attitude in the community at the beginning of the day, motivate residents, create camaraderie, and strengthen unity. Seminars are community-wide teaching sessions led by peers or staff presenting topics that directly or indirectly relate to the TC perspective on recovery and right living. House meetings are coordinated by senior residents to transact community business. General meetings take place only when needed and are usually called so that negative behavior, attitudes, or incidents in the facility can be addressed. While these activities are often facilitated by senior residents, staff are available to oversee them. Community enhancement also occurs in a variety of nonscheduled, informal activities as well. These include activities related to rituals and traditions, celebrations (e.g., birthdays, graduations, phase changes, job changes), ceremonies (e.g., those relating to general and cultural holidays), and memorial observances for deceased residents, family members of residents, and staff members.

63.2.3.6 Community and Clinical Management Elements

Community and clinical management elements maintain the physical and psychological safety of the environment and ensure that resident life is orderly and productive.

Thus, they strengthen community as a context for social learning. The main elements that are staff managed, although with some input from the senior resident social hierarchy, are privileges, disciplinary sanctions, surveillance, and urine testing. However, peer confrontation in the form of verbal correctives, affirmations, and feedback (e.g., reactions, advice, information) are ongoing community management activities.

63.2.3.7 Program Stages and Phases

Recovery in the TC is a developmental process that can be understood as a passage through program stages of learning. The learning that occurs at each stage facilitates change at the next, and each change reflects movement toward the goal of recovery. Three major program stages characterize change in long-term residential TCs – *orientation-induction*, *primary treatment*, and *reentry* – and may include additional substages or phases. The original time frame for these stages was grounded in a planned duration of treatment ranging up to 24 months. Current stage and phase durations are shorter commensurate with decreased overall planned durations. Regardless of temporal changes completion of each stage is a celebrated event marking acknowledged programmatic and clinical progress.

Completion marks the end of active program involvement. Graduation itself, however, is an annual event conducted in the facility for individuals who have completed all program stages and have successfully spent some time outside the treatment facility. Thus, the TC experience facilitates a process of change that must continue throughout life; and what is gained in treatment are tools to guide the individual on a path of continued change. Completion, or graduation, therefore, is not an end but a beginning.

63.2.3.8 Aftercare

TCs have always acknowledged the patient's efforts to maintain sobriety and a positive lifestyle beyond graduation. Until recently, long-term TCs addressed key clinical and life adjustment issues of aftercare during the reentry stages of the 2-year program. As noted, funding pressures have resulted in shorter planned durations of residential treatment and the stages and phases therein. This has underscored the necessity for aftercare resources to address both primary treatment as well as reentry issues. Thus, many contemporary TCs offer post residential aftercare treatment and social services within their systems, such as intensive day treatment and step-down outpatient ambulatory treatment, or through linkages with outside agencies.

63.2.4 The Effectiveness of Therapeutic Communities

Over the past four decades, a considerable scientific knowledge base has developed with follow-up studies on thousands of individuals treated in TCs. The most extensive body of research bearing on the effectiveness of addiction TC programs has amassed from field outcome studies. These all employed similar longitudinal designs that follow admissions to TCs during treatment and 1–5 years (and in one study up to 12 years) after leaving the index treatment.

These studies show that TC admissions have poor profiles in terms of severity of substance use, social deviance, and psychological symptoms. The striking replications across studies leave little doubt as to the reliability of the main conclusion. Namely, there is a consistent relationship between retention in treatment and positive posttreatment outcomes in TCs. Replication studies overseas seem to follow the same trend. This conclusion is supported in the smaller number of controlled and comparative studies involving TC programs (for a recent review of the TC outcome literature in North America, see De Leon 2010).

Overall, the weight of the research evidence from multiple sources (multi-program field effectiveness studies, single-program controlled studies, meta-analytic statistical surveys, and cost-benefit studies) is compelling in supporting the hypothesis that the TC is an effective and cost-effective treatment for certain subgroups of substance abusers, particularly those with serious social and psychological problems in addition to their drug abuse.

63.2.5 Adaptations and Modifications of the TC for Special Populations and Settings

The traditional TC model described in this chapter is actually the prototype of a variety of TC-oriented programs. Today, the TC modality consists of a wider range of programs serving a diversity of patients who use a variety of drugs and present with complex social and psychological problems in addition to their chemical abuse. Client differences as well as clinical requirements and funding realities have encouraged the development of modified residential TC programs with shorter planned durations of stay (3, 6, and 12 months) as well as TC-oriented day treatment and outpatient ambulatory models. Having become overwhelmed with alcohol and drug abuse problems, correctional facilities, medical and mental hospitals, and community residences and shelters have implemented TC programs within their settings.

Most community-based traditional TCs have expanded their social services or have incorporated new interventions to address the needs of their diverse residents. These changes and additions include family services, primary health care specifically geared toward HIV-positive patients and individuals with AIDS, aftercare services particularly for special populations such as substance-abusing inmates leaving prison treatment, relapse prevention training, components of 12-step groups, mental health services, and other evidence-based practices (e.g., cognitive-behavioral therapy, motivational interviewing). Mostly, these modifications and additions enhance but do not substitute for the basic TC approach, community as method. Research literature documents the effectiveness and cost-effectiveness of modified TCs for special populations including homeless mentally ill chemical abusers, those in criminal justice settings, and adolescents (e.g., De Leon et al. 2000; Sacks et al. 2008; Wexler and Prendergast 2010; Jainchill et al. 2005; De Leon 1997).

63.2.6 TCs Worldwide

Over some five decades TC programs have been implemented worldwide. In Europe, the establishment of drug-free therapeutic communities was the main treatment response to the emerging heroin problems in the 1960s and 1970s. The original American TC model was adapted to the European culture and it integrated the long-standing local traditions and influences. Between 1968 and 1983, the TC approach spread rapidly across virtually all countries in Europe including the United Kingdom and subsequently to Asia, Africa, and Latin America. Globally, it is conservatively estimated that there are over 3,000 TCs operating in hospital, prison, juvenile centers, outpatient, and community-based settings.

63.2.7 TC Outcome Research Worldwide

The North American research literature is the most extensive and has been briefly cited above. There is a modest but developing research literature on TCs worldwide particularly of European programs. The main conclusion from recent reviews of the European outcome studies may be briefly summarized.

"Length of stay in treatment and participation in subsequent aftercare were consistent predictors of recovery status. The authors conclude that TCs can promote change regarding various outcome categories. Since recovering addicts often cycle between abstinence and relapse, a continuing care approach is advisable, including assessment of multiple and subjective outcome indicators" (Vanderplasschen et al. 2013). Similar conclusions are obtained in outcome studies of TC programs in Peru and Thailand (Johnson et al. 2007, 2008), Australia, (Pitts and Yates 2010).

Although treatment process studies are few, emerging research has supported hypotheses concerning the generality of the perspective, model, and method of TC. Utilizing a common assessment instrument (the Survey of Essential Elements Questionnaire SEEQ; Melnick and De Leon 1999), these studies emphasize that differences exist between standard and modified TCs in essential elements within cultures but that the similarities in elements outweigh the differences across cultures (Dye et al. 2009; Goethels et al. 2011; Johnson et al. 2007, 2008).

63.2.8 Cultural Adaptations of the TC

Given the complexity of the TC as a social psychological approach, it is understandable that its implementation has been influenced by cultural context. Even within North America, for example, TC programs have adapted to ethnic diversity factors (De Leon et al. 1993). The adaptation of the TC to cultural diversity or context factors is still greater at the global level.

Beyond the above studies supporting the generality of the essential elements, there has been relatively little empirical research that focuses on cultural influences in the adaptation of the TC. However, a considerable descriptive literature of TCs in different cultures has unfolded over some four decades. Some reports can be found in scientific journals but most are contained in the published conference proceedings of international and regional TC associations, e.g., the World Federation of Therapeutic Communities (WFTC), the European Federation of Therapeutic Communities (EFTC), the Australasian Therapeutic Communities Association (ATCA), the Latin American Federation of Therapeutic Communities, and the Asian Federation of Therapeutic Communities.

These writings, along with the few empirical studies and the years of observations by trainers, consultants, and others, have indentified various cultural context influences that are embedded in TC programs (see some examples in Table 63.2). It is beyond the purview of this chapter to discuss these in detail, but several working conclusions are offered concerning the TCs adaptation to cultural influences.

First, the TC perspective (i.e., views of the whole person disorder, recovery, and right living) and its approach (community as method) can be preserved and integrated within diverse cultures. Second, empirical research is needed to abstract a more complete list of cultural influences and to assess their impact on outcomes. Finally, across all cultures, maintaining *fidelity* of practice is necessary to assure the optimal effectiveness of the TC approach, a general issue which is briefly discussed in the last section of this chapter.

63.2.9 Issues and Challenges to the TC

The evolution of the contemporary therapeutic community (TC) for addictions over the past 45 years may be characterized as a movement from the marginal to the mainstream of substance abuse treatment and human services. Currently TCs serve a wide diversity of clients and problems; they have reshaped staffing composition, reduced the planned duration of residential treatment, reset its treatment goals, and, to a considerable extent, modified the approach itself. These evolutionary changes have surfaced key issues that challenge the TC to maintain the integrity of its unique approach. Several of these are briefly highlighted: funding, workforce, research, treatment fidelity, and the diversity of TCs. Though interrelated, these issues are discussed separately.

63.2.10 Funding and Planned Duration of Treatment

Issue: The success of the TC approach has been demonstrated primarily for residential programs with planned durations of treatment of at least 9–12 months. In recent years, however, fiscal support has been steadily decreasing for long-term treatment in general and for residential treatment in particular. Thus, for the large

Table 63.2 Some examples of cultural elements shaping the unique TC characteristics in different cultures

Gender. In cultures where there are strict norms regarding the mixing of the sexes, there are separate TCs for men and women. The segregation is not driven by clinical rationale intended to better meet the unique needs of a particular gender but more for moral and reasons of propriety.
Religion. In most Eastern TCs, religion and religious practices are integrated into the TC structure. Those who belong to minority religions are encouraged to practice their faith. Major religious holidays are observed and program activities are tailored around celebrations of such holidays. Even dietary practices are observed.
Social organization. The traditional hierarchical structure of the TC is highly compatible with the formal and often rigid social structure in most conservative cultures. The TC hierarchical structure lends clarity which is consistent with the formal social structures of most of these societies. The delineation and lack of ambiguity of job positions and social status in the community promotes social harmony. It also defines the social roles of and expectations from the community members.
Role of the recovering addict as therapist. In most Oriental or Eastern cultures, academic credentials are preferred over experiential training. The contributions of the "recovering" person as therapist are not greatly appreciated, unless the person has a college degree in addition to personal experience. It requires a paradigm shift to consider, for example, a recovering addict or a recovered mentally ill person become therapists themselves.
Time orientation or temporal perception. Eastern culture has a fluid perception of time in contrast to Western society's highly structured time perception, "on time" versus "in time" orientation. Time orientation or how and when activities are implemented has implications in terms of operational efficiency and outcomes. The result-oriented and purpose-driven structure and schedule of the TC compel timeliness in order to comply with the demands and expectations of supporting and maintaining the community. Timeliness is observed across the board out of necessity, transcending cultural temporal perception.
The professional as TC staff. Many TCs outside the United States were founded by professionals who employed the services of TC-recovered ex-addicts as clinical staff along with professional staff. Working as a team, the combination creates a very progressive TC by exploiting the unique contributions of each.
Family. The importance of the family and their role in treatment in various cultures are evident in the popularity of family associations (Perfas 2012). Some TCs, such as in the case of Indonesia, were conceived by parents who originally sent their children to a Malaysian TC for treatment. In due time, they initiated a TC movement in their own country. Malaysian and Chinese TCs consider family and religion (spirituality) to be central to treatment (Bunt et al. 2010).

majority of TCs that depend upon public funding, planned duration of treatment has been reduced often *below the threshold* of time needed to yield positive outcomes. This adjustment to funding pressures potentially undermines the viability of the TC as a cost-effective modality in the health-care system.

63.2.11 Workforce

Issue: The expansion of the TC to serve special populations in special settings has resulted in a number of problems in the recruitment, retention, and development of experienced staff. General problems include low salaries, limited career goals, and difficult working conditions. However, a specific workforce issue arises from the

diversity of staff in TCs. The increased number of traditional professional staff from mental health and social services has posed a special challenge to the TC. Based on their education and training, traditional professional staff utilize concepts, vernacular, and methods that often counter or subvert the fundamental mutual self-help features of the TC. Moreover, most professionals and ex-addict paraprofessionals who work in TCs do not undergo rigorous and supervised training on the TC model and its practice.

63.2.12 Research

Issue: Despite decades of therapeutic community (TC) outcome research, some critics have questioned whether the TC is an evidence-based treatment for addictions. Given the relative lack of randomized, double-blind control trials, it is concluded that the effectiveness of the TC has not been "proven." Such conclusions contain serious implications for the acceptance and future development of the TC.

A new research agenda should build on the existing knowledge base that documents the contribution of the TC as a major health and human services modality. This agenda should include studies that demonstrate (a) *health and social benefits* (e.g., reduction in drug/alcohol use and social deviancy and increase in employment, education, and overall psychological well-being); (b) *cost-benefits* of both long-term TCs and shorter-term residential programs for specific subgroups of substance abusers; and (c) *collateral benefits* which refers to the *prevention* of trans-generational drug use, HIV, STDs, as well as family breakdown among treatment successes.

63.2.13 Treatment Fidelity

Issue: Understandably, TCs have pursued financial solvency by expanding to serve a wide variety of populations, e.g., mental health, homeless, corrections, juvenile justice, and child care. Contracts have obligated TCs to meet regulations of community, state, and federal agencies and often to incorporate practices based upon different professional views of treatment.

This expansion outward of the TC, however, has been at the expense of *inward* refinement of the approach itself. It is one thing to modify and adapt the TC for special populations, settings, and shorter durations of treatment. It is quite another to ignore the development of the TC's unique approach, *community as method*. Thus, if the TC is to retain its unique identity within mainstream human services, it must address the complex issue of treatment *fidelity*.

TC effectiveness and fidelity of treatment are closely related. High-fidelity treatment produces better outcomes (Dye et al. 2009). The key strategies needed to assure high-fidelity TCs are staff training based upon critical elements, teaching curricula grounded in a uniform definition of community as method, and appropriate training models that integrate didactic and experiential learning.

Table 63.3 Classification of TC programs

Standard TC programs. These are guided by the TC perspective, retain essential components of the program model, and utilize community as method as the primary approach. They are mainly housed in residential settings, with longer planned durations of treatments, serving the more severe substance abusers (primarily client driven).
Modified TC programs. These are guided by the TC perspective, incorporate essential components of the model, but adapt community as method for special populations (e.g., co-occurring disorders, criminal justice substance abusers, juveniles) and settings (hospitals, shelters, prisons). Key adaptations are more staff directed, greater emphasis on individual differences, moderated intensity of group process, and a more flexible program structure. Additionally, these programs incorporate strategies and services which have proven useful in addressing particular problems and special populations, including pharmacotherapy (e.g., methadone, buprenorphine, psychotropic medications) as well as varieties of counseling and family therapy (client and staff driven).
TC-oriented programs. These *are not* guided by the TC perspective and do not adhere to community as method. Typically, these serve less severe clients in short-term residential or day treatment settings and are eclectic in their approach. They select elements of the TC (e.g., community meetings, peer support group, etc.) but mainly utilize services and practices that are not specific to the TC (primarily staff driven).

63.2.14 Diversity of TC Programs

Issue: The TC approach and model has been successfully adapted and modified for various populations and settings. However, within the wide diversity of programs that represent themselves as TCs, many do not actually implement the TC approach that has proven successful. This often results in variable treatment outcomes and fosters misperceptions of the therapeutic community as an effective evidence-based approach. The credibility of the TC modality in health and human services will require classification of the diversity of programs as well as the development of standards of quality assurance.

63.2.15 Classification of TC Programs

The range of TC programs for substance abuse and related problems can be organized into three broad categories. These are based upon the extent to which a program is guided by the TC perspective (whole person, recovery, and right living), adheres to the approach (community as method), and retains essential components of the program model (see Table 63.3).

Thus, not all programs that label themselves as therapeutic communities are actually TCs. Clarification of differences in programs, the clients they serve, the goals of treatment, and the fidelity of the particular treatment strategies utilized, is necessary to preserve the integrity of the TC approach.

Finally, TCs worldwide are also undergoing many of the evolutionary changes described above, including modifications for special populations and particularly adapting to fiscal pressures to reduce time in residential treatment. A notable development is the rapprochement between the addiction TC and the psychiatric TC pioneered by Maxwell Jones that has been prominent in Europe. Both of

these TC approaches share many of the common elements of community as method to treat populations with both substance use and personality disorder. Nevertheless, maintaining uniformity and fidelity of the TC approach in light of these changes remains a challenge.

63.3 Conclusion

Arguably, the therapeutic community for addictions (TC) is the first formal treatment approach that is explicitly *recovery oriented*. Surely, AA and similar mutual self-help approaches facilitate recovery but these represent themselves as support, not treatment. Pharmacological approaches, notably, methadone maintenance, have as their treatment goal the reduction or elimination of illicit opiate use; and behavioral approaches, such as cognitive-behavioral therapy (CBT), contingency contracting, and motivational enhancement (MET), focus upon reduction, and not necessarily abstinence and recovery, in targeted drug use. In the TC perspective, however, the primary goal of treatment is *recovery* which is broadly defined as changes in lifestyles and identities.

Thus, in the current context of substance abuse policy and issues (e.g., various treatment options, harm reduction strategies, the economic pressures on health care), the overarching challenge of the TC is to reassert its unique place and mission – that of promoting recovery and right living.

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Spiritual Aspects of the Twelve Step-Method in Addiction Treatment

64

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Contents

Abstract

This chapter is directed at defining the nature of spirituality and its relationship to empirical research and clinical practice. A preliminary understanding of the spiritual experience can be achieved on the basis of diverse theoretical and empirically grounded sources, which will be delineated. Furthermore, the impact of spirituality on addiction in different cultural and clinical settings is explicated by illustrations of its application with regard to Alcoholics Anonymous.

64.1 Introduction

64.1.1 AA as a Spiritual Recovery Movement

How does spirituality relate to recovery from addiction? There is a parallel between the way attitudes are transformed in intensely zealous groups and the way the denial

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of illness and the self-defeating behaviors of alcoholics and drug addicts may be reversed through induction into Twelve-Step groups like AA.

Members of the lay public may conclude that certain healthcare issues are inadequately addressed by the medical community, particularly when doctors are not sufficiently attentive to the emotional burden that an illness produces. When mutually supportive groups of laymen coalesce to implement a response to this perceived deficit, they may form a spiritual recovery movement (Galanter 1997), one premised on achieving remission based on beliefs independent of evidence-based medicine. Such movements may ascribe their effectiveness to higher metaphysical or nonmaterial forces and claim to offer relief from illness.

AA can be considered as a highly successful example of a spiritual recovery movement, as such movements have three primary characteristics. They (a) claim to provide relief from disease, (b) operate outside the modalities of established empirical medicine, and (c) ascribe their effectiveness to higher metaphysical powers. The appeal of such movements in the contemporary period is due in part to the fact that physicians tend not to attend the spiritual or emotional concerns of their patients (Galanter 2005).

Clearly, the attitudes and behavioral norms that AA espouses are much more in conformity with the values of the larger culture than those of zealous religious sects. The expectation of avoiding drunkenness in AA, normative in our culture, illustrates this. People who are highly distressed over the consequences of their addiction are therefore candidates to respond to the strong ideologic orientation of AA toward recovery and are operantly reinforced by the relief produced by affiliation with the group's ideology and behavioral norms, all related to abstinence and a spiritually grounded lifestyle. Significantly, AA generates distress in its members by pressing them to give up their addictive behaviors, but the distress associated with this conflict is relieved if they sustain affiliation and cleave to the group.

64.2 Spiritual Aspects

64.2.1 Spirituality as a Psychological Construct

Two empirically grounded perspectives have played a material role in framing how we conceptualize recovery. One derived from a model of psychopathology modeled on the work of Emil Kraeplin (1902). He framed an approach that now characterizes the contemporary medical model for mental disorders, categorizing disease entities diagnosed on the basis of explicit and discrete symptoms. This approach is evident in the development of criteria for substance use disorders employed in recent editions of the symptom-based Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association 2000). From this perspective, a state of remission, colloquially called recovery in rehabilitation circles, can take place with the resolution of the specific symptoms listed as diagnostic criteria. A second perspective on recovery derives from behavioral psychology, whose model of stimulus-response sequences has led to the ordering of experience around discrete

phenomena that can be observed by a researcher or clinician. From this perspective, recovery can also be defined in terms of observable, measurable responses to substance use, lending credence to recovery as a process defined in behavioral terms.

Both perspectives are well suited to the study of psychopathology and have lent the addiction field approaches to studying addiction as a disorder, one that is compatible with research approaches employing experimental controls that are used in the physical and biological sciences. Both have therefore had heuristic value in promoting a research field that has yielded many advances in addiction treatment. There is a third perspective, however, that is defined on the basis of addicts' reports of their own subjective experience. These experiences are not directly observable by the clinician but are available only as reported through the prism of the person's own introspection and reflection. This model is more difficult to subject to measurement, but instruments are being developed that can be applied for its study, as will be discussed below. This approach is inherent in the spiritually oriented psychology of Carl Jung (1978), who had a direct influence on Bill W's framing of the Alcoholics Anonymous ethos (Cheever 2004). William James (1929), often described as the father of American psychology, also discussed mental phenomena in terms of subjectively experienced mystical or spiritual experience. (In fact, he wrote that "the drunken consciousness is one bit of the mystic consciousness" [p. 378].) The need for spiritual redemption was vital in the writings of Viktor Frankl, who wrote *Man's Search for Meaning* (1984), and has recently been espoused with regard to psychotherapy by William Miller (1999).

This third perspective is related to the model of spiritually grounded recovery we will discuss here, insofar as it emphasizes the achievement of meaningful or positive experiences, rather than a focus on observable, dysfunctional behaviors. Research on this third approach would typically rely on self-report scales, such as those which can be facilitated by development of instruments like the Life Engagement Test (Scheier et al. 2006); the General Well-Being Schedule (Dupuy 1972); or our own Spiritual Self-Rating Scale (Galanter et al. 2007). We will consider its role in AA, models for how it takes place, and ways it can be measured. In this respect, recovery can be understood as a process whereby an abstinent addicted person is moving toward a positive adaptation in life. This movement can take place with varying degrees of success, depending on the person's own innate capacities and the circumstances in which they find themselves.

64.2.2 Spirituality and Religious Experience

The relative role of spiritual experience in the Twelve-Step recovery process has been investigated from a variety of perspectives, generally in relation to patients' experience in AA. Kelly et al. (2009) reviewed studies that applied mediational tests to ascertain how AA achieves beneficial outcomes and found little support for a role of AA's specific spiritual mechanisms. In fact, with regard to religiosity, Tonigan et al. (2002) found that, although atheists were less likely to attend

AA meetings, those who did join derived equal benefit as did spiritually focused individuals. On the other hand, in one study on persons recovering from cocaine dependence (Flynn et al. 2003), respondents attributed their positive outcomes to religion and spirituality. Additionally, Zemore (2007) followed up a large sample of substance abusers 1 year after inpatient treatment and found that increases in spirituality contributed to the increment in total abstinence associated with Twelve-Step involvement.

Our own experience, as well, is compatible with these findings, as we have found in multiple settings (Galanter et al. 2012, in press a, b) that spirituality is integral to recovery in Twelve-Step groups. This was particularly evident among long-term members.

64.2.3 Spiritually Grounded Recovery in AA

The AA "program of recovery" is mentioned in numerous places in the Big Book, *Alcoholics Anonymous* (Alcoholics Anonymous World Services 1955), and is associated there with terms such as "spiritual experience" and "spiritual awakening" and with working AA's Twelve Steps. Four of the steps include the word God, which is qualified "as we understood Him." Some clarity is lent to this latter phrase in the Big Book where it is pointed out that "with few exceptions, our members find that they have tapped an unsuspected inner resource which they presently identify with their own conception of a Power greater than themselves" (p. 569–570). Flexibility on the issue of theistic belief is also made clear in one chapter that addresses any alcoholic person "who feels he is an atheist or agnostic," encouraging their membership as well. The text points out for these members that even "We Agnostics. . .had to face the fact that we must find a spiritual basis for life" (p. 44) in order to achieve recovery, implying therein the fellowship's distinction between spirituality and theistic religion.

This issue of theistic connotation, however, is as yet resolved relative to the judicial system, where the application of AA is sometimes constrained because of potential church/state conflicts. It is open to question, however, whether the theistic connotations of AA can be modified without vitiating the program's effectiveness. In this relation, it should be noted that in a 5-year follow-up of recovering cocaine-dependent patients, the strength derived from religion and spirituality significantly distinguished between those who had a highly favorable outcome from those who did not (Flynn et al. 2003). Additionally, attendance at religious services distinguished significantly between criminal justice clients referred for substance abuse treatment who had a positive outcome and those who did not (Brown et al. 2004).

Spirituality among long-term members is likely instrumental in sustaining the integrity of the fellowship itself. The prominence of spiritually committed long-term members at meetings, and their availability to serve in the sponsorship role creates readily available models for earnestly held sobriety. They serve as role models for believing commitment to the Twelve-Step spiritual ethos to help

newcomers achieve stabilization in membership. Nonetheless, some people attending NA meetings may find it hard to identify with the spiritual orientation of long-term members.

In the clinical context, recovery is based on a person's behavioral and physiologic status, which can be assessed by recourse to criteria employed in the DSM. Some of these criteria are also embodied in the Addiction Severity Index (McLellan et al. 1992), which is employed widely in research to evaluate recovery. These items can be assessed relatively easily, as they are premised on observable behavior or delineated by symptomatology described by patient, family member, or clinician.

A spiritually grounded definition of recovery, however, can be useful as well. Such a concept relates to the importance of non-demographic subject factors, originally proposed as "quality-of-life" issues (Campbell et al. 1976) – among which spirituality can be considered. In this context, a series of suitable criteria for "diagnosing" addiction (a more apt term than "substance dependence") could be developed. They could then be used to assess the spiritual aspect of recovery associated with the Twelve-Step experience. Resolution of these issues could be considered as important to the spiritual aspect of recovery from addiction. A series of criteria could include items such as:

- Loss of sense of purpose due to excessive substance use
- A feeling of inadequate social support because of one's addiction
- Continued use of a substance while experiencing moral qualms over its consumption
- Loss of the will to resist temptation when the substance is available

Another aspect of the DSM format can be considered as well. The manual stipulates "course specifiers" of remission such as "on agonist therapy" and "in a controlled environment." These are included because they are explanatory to the clinician. To them could be added "fully engaged in a program of Twelve-Step recovery," which would be equally explanatory to many clinicians.

But are spiritually grounded criteria measurable? In recent years, methodologies have been developed and validated that could be used to assess outcome based on such subjectively experienced criteria. They employ a systematic approach to measurement and can be used to describe spiritually related states:

A. **Affective state:**
   (i) A sense of well-being, measured by the General Well-Being Schedule (Dupuy 1973) (which we employed) or the Subjective Happiness Scale (Lyubomirsky and Lepper 1999).
   (ii) Contentment with one's life circumstances, measured by the Satisfaction with Life Scale (Diener et al. 1999).
   (iii) Positive affect, assessed with the Positive and Negative Affect Schedule (Watson et al. 1988), dealing with both variables as separate dimensions, rather than bipolar ends of the same scale.
   (iv) Feelings of support, employing a Scale for Perceived Social Support (Cohen et al. 1985).

B. **Existential variables:** Meaningfulness in one's life: assessed by the Purpose in Life Test (Crumbaugh and Maholick 1969).

C. **Flow**: The experience associated with engaging one's highest strengths and talents to meet achievable challenges, as measured by Experience Sampling (Csikszentmihalyi and Larson 1987) or the Flow Scale (Mayers 1978).
D. **Spirituality:** The Spirituality Self-Rating Scale, which we developed and applied to both substance-abusing and non-substance-abusing populations (Galanter et al. 2007), as well as other such scales. By means of our own scale, we were able to distinguish different populations of substance abusers' level of spiritual orientation from the of non-substance populations.
E. **Personality assessment**: The Classification of Strengths (Peterson and Seligman 2004), a series of characteristics based on categories of moral excellence drawn from observations across different cultures.
F. **AA involvement:** Measures of the degree of affiliation and commitment to the AA fellowship (Humphreys et al. 1998).

A methodology for defining recovery based on measurements like these may not have the same appeal to biomedically oriented clinicians as does the conventional symptom-based approach, as these measurements are based on self-report of the person's subjective state. Furthermore, the enthusiasm of newfound recovery may yield a Hawthorne effect. The biomedical format currently applied in diagnosis derives from the school of Kraeplin and subsequent investigators like those who developed the Feighner criteria (Feighner et al. 1972) in the 1970s and then in the ensuing DSM system. Spiritual variables, however, have a lineage as well, from William James, Carl Jung, and Bill W.

64.2.4 AA in the Professional Context

The spiritually oriented Twelve-Step approach has been integrated into professional treatment in some settings where it serves as the overriding philosophy of an entire program or, in others, where it is one aspect of a multimodal eclectic approach. The Minnesota Model for treatment, typically located in an isolated institutional setting, is characterized by an intensive inpatient stay during which a primary goal of treatment is to acculturate patients to acceptance of the philosophy of AA and to continue with AA attendance after discharge (Cook 1988). Although a variety of exercises are included during the stay, this approach has been criticized as dogmatic because of its sole reliance on the Twelve-Step approach. The outcome of this model, however, has been shown to yield positive results in a survey of patients discharged from one such setting (Hazelden, in Center City, MN) (Stinchfield and Owen 1998), but randomization of patients treated in Minnesota Model facilities with those treated by means of an alternative approach is needed.

A more eclectic option is illustrated in the integration of Twelve-Step groups into a general psychiatric facility for the treatment of patients dually diagnosed for major mental illness and substance abuse. The importance of spirituality in such a highly compromised population was evidenced in our studies (Galanter et al. 2007) in which such patients ranked spiritual issues like belief in God and

inner peace higher than tangible benefits like social service support and outpatient treatment. One inherent advantage of this format is that it benefits from the introduction of an inspirational approach to patients who, as Goffman has pointed out (1963), have become "degraded" by stigmatization due to their psychiatric disorders.

In summary, spirituality is a matter of personal meaning that is widely accepted. It is also central to the recovery process from addiction for many AA members. The fellowship of AA, in fact, can be considered a movement developed in relation to people's spiritual needs. Although spirituality is subjectively experienced, it can be assessed systematically in given individuals by employing currently available empirical techniques. By such means, an important aspect of addiction recovery can be defined and studied.

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Danshukai and Other Support Groups in Addiction Treatment

65

Atsushi Yoshimura and Susumu Higuchi

Contents

Abstract

Japan has rapidly developed in the economic field following World War II. Simultaneously, alcohol and drug dependence have been serious problems for several decades. To deal with such problems, indigenous self-help and mutual-help organizations for alcohol and drug dependence have been founded and developed.

Danshukai is the most widely spread organization of self-help and mutual help for alcohol dependence throughout Japan. Its early activities were inspired by AA (Alcoholics Anonymous) and have been translated into the Japanese context. The membership of Danshukai has reached double the number of AA participants in Japan but has gradually tapered off in recent years. The consistent slogan of Danshukai is "one-day abstinence," which means that the members promise themselves that they will not drink alcohol on that day.

The DARC (Drug Addiction Rehabilitation Center) system was developed originally in Japan. DARC was formed as a rehabilitation facility with a community of drug-dependent associates in Tokyo. Such communities have been formed in many cities in Japan. The activities of DARC not only have

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extended to the rehabilitation for drug dependence but also encompass the approach to various drug addiction problems, such as consultation for and education in drug problems.

65.1 Introduction

Alcohol and drug misuse have created social, medical, and economic problems for several decades in Japan. Both formal and informal interventions for these problems have been conducted. Many facilities have developed systems to meet the therapeutic needs associated with alcohol and other drug misuse.

Japan has a particular language, culture, and tradition. In earlier eras, the Japanese were gifted at translating various cultures from China or Western countries into the Japanese context. These trends have been inherited by modern Japanese society and systems. Rehabilitation programs and organizations aimed at treating alcohol and drug addiction in Western countries have been modified to suit the Japanese context. Particular mutual aid support groups for alcohol and drug addiction also spread throughout Japan. Here, we introduce these distinctive mutual-help organizations in Japan.

65.2 Support Groups

65.2.1 Danshukai

In Japan, there are currently two major self-help groups for alcohol-dependent individuals. The first is AA (Alcoholics Anonymous), which was introduced from the United States. The second is the Japan Sobriety Association "Danshukai," which is an indigenous and distinctive organization in Japan.

Danshukai was founded in the city of Kochi in November 1958 and has spread throughout Japan since 1965. Its early activities were inspired by AA and have been translated into the Japanese context. The number of members reached approximately 10,000 individuals at the beginning of the 2000s, which was double the number of AA participants in Japan. However, the number of Danshukai participants reached a plateau and has gradually tapered off in recent years, partly because the number of medical institutions treating alcohol dependence has increased and an extended medical support system has been developed for alcohol-dependent patients. In April 2012, the number of Danshukai members decreased to 8,500 (Zendanren 2013). The members belong to one of the 556 nationwide community-level "Danshukai." Most cities and towns have one or more of these community-level Danshukai. Therefore, knowledge of Danshukai for alcohol-dependent individuals has spread widely among the general public, although the precise roles and activities are not necessarily known.

Instead of the 12 steps of AA, Danshukai has 7 principles (Zendanren 2012):

1. We should confess that we are helpless against alcohol and that we could not do anything by ourselves.

2. We should attend regular meetings and speak about ourselves honestly.
3. We should remember our past experiences and failures that have been caused by alcohol. We should gain insight about ourselves by listening to other members' experiences.
4. We should respect others' personalities and realize that we can remain abstinent through our connections and trust in the group.
5. We should try to reform ourselves and create a new life.
6. We should provide compensation to our family and to those whom we have troubled.
7. We should speak about our pleasure in remaining abstinent to others suffering from alcohol harm.

AA emphasizes the need for a "higher power" to recover from failures caused by alcohol. Many Japanese cannot easily accept religious concepts based on Christianity, since many Japanese believe in polytheism. Therefore, Danshukai does not underscore the importance of religious power, but instead emphasizes the mutual help and unity provided by the group and the importance of compensation for the members' family. The concept of Danshukai is more familiar to Japanese people. This is one of the primary reasons that Danshukai activities have spread throughout Japan.

Danshukai has several original characteristics, compared with AA (Higuchi and Kono 1994). Danshukai has been incorporated and administrated by fees from members and external financial assistance. The activities of Danshukai have been supported by the Health Care Authorities in each district. Danshukai has a strict hierarchy system from the community level to the national level. Daily activities are at the center of each community-level Danshukai, which consists of several members to dozens of members. These community-level Danshukai belong to a prefectural Danshukai that in turn belongs to the All-Japan Federation. Danshukai at each level elect a president and executives, and they independently administer each community group and hold meetings (Table 65.1).

While AA meetings are strictly anonymous, Danshukai demand that participants introduce their names to the community. Danshukai members believe that exposing oneself, including one's name, one's family, and one's private life, is essential to recovering from alcohol dependence. The attendance of family members is also encouraged, because Danshukai consider spouses to play a major role in the continued abstinence of alcohol-dependent individuals. The attendance of couples facilitates communication, resulting in the recovery of family relationships. These philosophies of Danshukai are familiar to middle-aged and elderly men, especially in the rural areas. There were 3,800 family members (primarily wives) participating in Danshukai in 2012.

On the other hand, alcohol-dependent women and adolescents are inclined to resist the philosophy of Danshukai. The number of female members was about 800 in 2012. Only 160 Danshukai members had enrolled while they were in their teens or 20s. In 2012, only 47 Danshukai members were in their 20s, and none of the members were in their teens. The decrease in membership has become one of the greatest problems faced by Danshukai. Their philosophy and system must adapt to

Table 65.1 Comparison between Danshukai and Alcoholics Anonymous in Japan

Characteristics	Danshukai	Alcoholics Anonymous
Members	Approximately 8,500	Approximately 4,700
Basic policies	Attendance at regular meeting	Attendance of meetings
	"One-day abstinence"	Twelve steps and twelve traditions
Spirituality	The unity and solidarity in the community are emphasized	A "higher power" that is greater than the individual is respected
Anonymity	Non-anonymity	Anonymity
Family	Families are encouraged to attend meetings	Al-Anon are held for family members
Establishment	Founded in Kochi city in November 1958	Founded in Tokyo in March 1975
Activity	Activities have expanded nationwide. Support has been obtained from Health Care Authorities	Activities have spread to peoples of various social levels, but are still limited to large cities
Organization	Danshukai is incorporated and is operated as an organization, forming a hierarchical system	AA has a flat organizational structure
		Local committees are formed by representatives of each group
Financial base	Fees from members	Contributions by members
	Financial assistance and donations from external sources	Sale of publications
		No financial assistance or donations from external sources are accepted
Office	Federation of Japan Sobriety Association, Tokyo	AA Japan General Service Office (JSO), Tokyo

meet the needs of the times. Danshukai has started activities to increase the number of members. They have held meetings for alcohol-dependent women only. Recently, they have received alcohol-dependent adolescents with multiple problems, such as drug dependence or eating disorders. Moreover, Danshukai meetings have been frequently held in the afternoon for retired members or unemployed members who are free during the daytime. Those who have physical disabilities or gait disturbances can also easily attend the daytime meetings (Wake 2013).

One of the most important tasks of members is to attend regular meetings. Meetings are usually informal and almost all are open (i.e., available to anyone). Members talk about their stories caused by drinking. While feature discussions are sometimes held, general discussions account for most of the meeting time. The core regulation of the meetings is "just speaking and listening." The members talk about their present condition or problems with alcohol in turn, and others must not interrupt their speech. Other members, except for the speaker, just listen. In principle, they are not allowed to criticize or encourage, even if the speakers confess their re-drinking or complain of their circumstances. Just talking about one's self and just listening to other members' speech lead to a sense of relief and an awareness that they have similar alcohol problems. Members can share the recognition that the troubles caused by alcohol are not unique to themselves, helping them to realize that they are not alone. Members can begin to help each other,

because they are companions who have undergone similar catastrophes. The sense of solidarity and responsibility is a motivating power to prevent members from drinking. AA members are encouraged to find an experienced individual, called a sponsor, who can help them to understand and follow the AA program. Although Danshukai members do not have such a sponsor, they receive mutual help as well as advice and support from other members as needed.

Regular meetings are held once every day, once a week, or once a month. The frequency of meetings is arbitrarily decided by each community-level Danshukai. A member is able to join a meeting held by another community apart from their home-affiliated community. Therefore, members in urban areas can easily attend meetings held in different spots. Members who have just started abstinence or who are continuing to drink are recommended to take part in meetings more frequently to avoid drinking. Through the meetings, members are able to recover their sensitivity and develop social skills.

The other important task is to maintain "one-day abstinence," which is a consistent slogan of Danshukai. Although abstinence should be maintained as long as possible, it is very difficult for alcohol-dependent individuals to achieve such a goal. To maintain abstinence, members pledge "one-day abstinence," which means that they will not drink alcohol on that day. Maintaining "one-day abstinence" can result in lifetime abstinence. Today, Danshukai members are trying to maintain abstinence by pledging "one-day abstinence."

Little evidence of the efficacy of Danshukai is available. Since participation in Danshukai meetings is voluntary and is not randomly allocated, a controlled study is very difficult to do. Two opposing self-selection biases may exist: (1) participants in Danshukai might have sufficient motivation to change their drinking habits, and (2) participants in Danshukai might have severe and refractory alcohol problems.

A longitudinal follow-up study of 133 alcohol-dependent Danshukai members was previously conducted in a rural area in Japan (Doi 1987). The ratio of newcomers who attended more than three meetings was 45.6 % during a 10-year period. More than half the members dropped out after participating in the meetings only once or twice. Twenty-five of the 133 participants who attended more than three meetings remained abstinent for over 2 years. The ratios of attendance and abstinence were relatively high, compared to another longitudinal follow-up study of AA meetings (Pagano et al. 2013), partly because medical staff played a role in the study. Eighteen of the 133 attendants died during the 10-year period.

65.2.2 DARC (Drug Addiction Rehabilitation Center)

In Japan, drug dependence is also a serious problem, in addition to alcohol dependence. Amphetamines and methamphetamines have been the most widely used illegal drugs. Recently, the use of new strong composite types of illicit compounds, which are comprised of various ingredients such as cocaine, heroin, marijuana, and so on, has begun to spread among young people in urban areas. Benzodiazepines are popular among various generations, especially among

individuals with serious anxiety and depressive moods. Actually, drug dependence has long been a problem in Japan, dating back to the 1950s.

DARC is an acronym for "Drug Addiction Rehabilitation Center." DARC consists of rehabilitation facilities for drug-dependent individuals (Tokyo DARC Support Center 2010). DARC members can use the facilities to recover from drug dependence over the course of several months to years. Members are able to receive physical, mental, and social support from DARC while they learn to live without drugs.

DARC was founded in 1985 by a drug-dependent patient. The patient provided an old house in Tokyo and formed a community with other drug-dependent associates (Kondo 2000). They started a rehabilitation program for drug dependence in their community. The program was a modification of the 12 steps of AA and emphasized group meetings. The goal of the program is not only to stop drug use but to recover their human nature, such as expressions of sympathy, kindness, and honesty. As of 2013, about 50 communities exist around Japan. The activities of DARC are independently practiced in each community. This diversity of activities among each community is an outstanding characteristic of DARC.

Member candidates of DARC are introduced through many pathways including lawyers, police officers, welfare, psychiatric hospitals, public health centers, and so on. Some members voluntarily enter DARC on their own. In many cases, they are brought to DARC by their families. About 90 % of the members have experienced medical care for a drug-related problem. About 70 % have been arrested prior to participating in DARC. Members in their 20s or 30s account for 80 % of DARC members. Usually, 12–13 years since their first drug use have elapsed at the time of a member's first DARC meeting (Nishimura 2004).

DARC members must generally live jointly with other members in a community house for 3 months to over 1 year and complete the residential program. They can then attend DARC meetings after they have left the community house. Members must pay a fee every month. The activities of DARC are administered using the membership fees. Since anonymity must be maintained within the community, DARC members use nicknames when speaking with each other. All members have an equal status in DARC and are free from social positions.

The only rule of DARC is regular participation in the meetings. Members are obliged to participate in morning meetings, afternoon meetings, and evening NA (Narcotics Anonymous) meetings. DARC is strongly connected to NA. Members are recommended to continue attending NA meetings after the completion of the DARC program. DARC does not necessarily force its members not to use drugs, but it encourages them to cultivate their independence and responsibility.

Even if members encounter problems, such as the reuse of drugs, they must participate in the meetings and tell their problems to the other members honestly. In their relationships with other members, they can share their distress, loneliness, and emptiness that resulted in their drug use or that were caused by drug use. They are also able to acquire the ability to communicate with others and to experience alternative lifestyles without drug use through the DARC program. The slogan of DARC members is "just for today," which means not using drugs today and doing their best today. Today without drugs will certainly lead to a clean future.

Table 65.2 Role and activities of DARC

Social	1. Nongovernmental organization
	2. Enlightenment of general public regarding drug problems
	3. Reduction of social and economic losses
Medical	1. Community for the treatment of drug dependence
	2. Awareness regarding the necessity of rehabilitation for individuals with drug dependence
	3. Information center for drug problems
	4. Primary care for drug dependence
	5. Training of counselors for mutual help
Judicial	1. Diversion from restraint to rehabilitation for drug dependence
	2. Support of defense for crimes caused by drug use
	3. Care program after release from prison
Welfare	1. Transition support for employment or schooling
	2. Consultation for drug problems
	3. Cooperation with the public administration
Educational	1. Education of risk for drug use to students
	2. Instruction regarding coping with drug problems to teachers or school staffs

Many members drop out of the program and return to a drug-dependent lifestyle. However, any member can resume the DARC program whenever they decide to stop drug use once again. DARC does not exclude those who slip into the reuse of drugs. Less than 1 % of the members have never resumed drug use after taking part in DARC. However, 30–35 % of members continue to attend NA meetings, even if they resume drug use several times along the way (Kondo 2000). Some members can become staff members who manage the DARC program after the completion of staff training. The staff and program members are equal and support each other to prevent drug reuse.

DARC also addresses various addiction problems. Therefore, the role of DARC has extended into various fields (Table 65.2). Members have spoken about their experiences with drug use in schools to prevent young people from using drugs. DARC has trained some members to be addiction counselors who can sympathize with people who cannot help being addicted to drugs. Through such campaigns, the activities of DARC have become known among medical, judicial, and educational staffs. The outlook of DARC emphasizing rehabilitation has spread, and DARC activities are expected to expand throughout Japan so that many people who suffer from drug dependence can participate in rehabilitation programs to recover, instead of being isolated in prisons or hospitals. Such interventions are critical for those who are afflicted with drug abuse.

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Addiction Recovery in Services and Policy: An International Overview

66

Alexandre Laudet and David Best

Contents

Abstract

This chapter provides an overview of the sweeping changes occurring in the addiction field in the United States and abroad, with special emphasis on the growing focus on recovery as the goal of services and the guiding vision of drug policy. "Recovery" goes well beyond substance use patterns to encompass improved functioning in life areas impaired by active substance use, as well as improved overall quality of life. Because research shows that substance use disorders are often chronic, recovery is

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conceptualized as a process that unfolds over time and requires a continuing care approach. We describe emerging service models including Recovery-Oriented Systems of Care (ROSC) and peer-driven recovery supports and review the implications of this new orientation for service providers and evaluation research. We conclude with some recommendations on strategies that medical professionals can use to promote recovery among substance-using patients.

Keywords
Recovery • Peer support • Addiction • Treatment

66.1 Introduction

As healthcare is changing on a number of fronts, healthcare professionals are grappling with new systems and care models while continuing to diagnose and treat human conditions that are, in many cases, as old as the human race. Substance use, abuse, and dependence is likely one such condition. However, the way society views it has changed over time – from moral failing or crime to chronic brain disease (McLellan et al. 2000). Parallel with these changes come changes in how addiction is addressed by systems and healthcare providers. In this chapter, we describe and discuss the increasingly popular "recovery" orientation to substance use problems: a model where the desired outcome goes beyond changes in substance use to a broader notion of improved personal functioning and quality of life. After describing the model and corresponding services, we end with a brief discussion of consequences of this new orientation for healthcare professionals.

66.2 Recovery Becoming Guiding Vision of a Substance Use Services and Policy

Treatment systems addressing substance use disorders (SUDs) and the federal agencies regulating them (e.g., in the United States, SAMHSA – the Substance Abuse and Mental Health Services Administration) have begun to effect a shift in their emphasis, with recovery becoming the guiding framework. There are two key, empirically based elements to this paradigmatic shift: the reconceptualization of SUD as chronic disorders and the broadening of what "recovery" means. First, research in the past decade has suggested that addiction is best conceptualized as a chronic disorder on par with other chronic conditions such as diabetes, asthma, or hypertension (McLellan et al. 2000). However, unlike these other conditions, treatment for substance use disorders (SUDs) has historically been delivered and evaluated using an acute care model: intense episodes of care during which a person, often in crisis, is assessed, treated, and released – ideally "cured" – all in a relatively short time (Dennis and Scott 2007). Growing evidence for long addiction and treatment "careers" consisting of multiple cycles of intensive and

costly treatment episodes (Dennis et al. 2005) followed by return to active addiction (Scott et al. 2005) has led to the conclusion that the acute care model is ill suited to address SUD as a chronic condition (Hser et al. 1997; McLellan et al. 2005a; O'Brien and McLellan 1996). Noting the disappointing outcomes of the current system and the many similarities between SUD and other chronic illnesses, the Institute of Medicine and leading addiction researchers have called for SUD treatment to shift from the acute care model to one of recovery management akin to the chronic care model used in the treatment of other chronic conditions (Dennis and Scott 2007; Humphreys 2006; Institute of Medicine 2005; McKay 2005; McLellan et al. 2000; Miller 2007; White et al. 2002, 2005b). A continuum of care model consistent with chronic disease is also aligned with the experience of persons in recovery who overwhelmingly describe recovery as "a process" vs. "an end point" (Laudet 2007).

The second element of the paradigmatic shift to a recovery orientation is rooted in the growing recognition that recovery goes well beyond making changes in one's substance use patterns (see next section). McLellan and colleagues may have put it best where stating: "typically, the immediate goal of reducing alcohol and drug use is necessary but rarely sufficient for the achievement of the longer-term goals of improved personal health and social function and reduced threats to public health and safety – i.e., recovery" (McLellan et al. 2005b, p. 448). Thus, the emerging recovery-oriented model of care provides a continuum of service and support designed to promote and sustain improvements in substance use (abstinence or significant reductions) and psychosocial functioning. This recovery framework reconciles a public health response to chronic care with a strength- and community-based focus that places the individual at the heart of their own recovery journey and emphasizes personal empowerment and individual ownership of the definition of and pathway to recovery. Promoting recovery requires giving individuals the tools and strategies to develop "capital," a strength-based approach that has gained prominence in both psychology (Seligman 2003) and criminology (Ronel and Elisha 2011) and is embodied in the addiction field by the construct of "recovery capital" (Granfield and Cloud 2001).

The emerging emphasis on recovery in addiction services is paralleled by a similar shift at the federal policy level. In the United States, the President's National Drug Control Strategy emphasizes the importance of promoting recovery, regardless of pathway (Office of National Drug Control Policy 2011) and calls for the expansion of recovery support services across community-based settings. The White House Office of National Drug Control Policy (ONDCP, the so-called drug tsar office) has also begun several interagency initiatives that emphasize the centrality of the recovery orientation to addressing SUDs, the need for recovery support services, and the importance of eliminating legal barriers to recovery (e.g., restrictions on housing and student loans for persons with a drug-related criminal history). For example, ONDCP is working in the US Department of Education that adopted the goal of providing a continuum of recovery supports at all levels in academic settings (Dickard et al. 2011). ONDCP has created a Recovery Branch to coordinate these efforts and engage federal partners, state

and local governments, membership and advocacy organizations, service providers, and other stakeholders in the design and development of policies, systems, services, communication campaigns, and other activities that support long-term recovery (Office of National Drug Control Policy 2011).

The growing emphasis on recovery-supportive services and policy unfolding in the United States is also observed in other countries. The United Kingdom is undergoing its own system transformation at the service and policy levels (Best 2012; United Kingdom Drug Policy Commission Consensus Group 2007). The UK Home Office that oversees most drug and alcohol policy in England and Wales has endorsed recovery as a goal of treatment services (HM Government 2010). That has been seen as a core component of the government "personalization" agenda, although the impetus for change has arisen in part from a dissatisfaction with the effectiveness of drug treatment in England and Wales (Easton 2008; McKeganey 2010). This shift in the United Kingdom followed an earlier change in Scotland, whose government's "Road to Recovery" (Scottish Government 2008) is a blueprint to system transformation. The origins of SUD recovery orientation were different in Scotland from England, with the policy document citing the success of the mental health recovery movement in Scotland, in particular its coordinating organization, the Scottish Recovery Network (Scottish Government 2008). In England, the policy shifts reflect the unique recovery context – i.e., the mounting critique of a treatment system predicated on low-intensity treatments (Best 2012) and a dissatisfaction with the prevailing treatment system and philosophy. In both countries, this was combined with a growing awareness of the burgeoning US recovery movement and a baseline of recovery activity in mutual aid and therapeutic communities to drive practice and policy change.

Most recently, seeds of transformation are also being planted in the Australian state of Victoria where the second author (DB) is spearheading a growing number of recovery initiatives including the promotion of policy change, the challenge of stigma through recovery walks and other events, and the development of a -university-based teaching and research program on recovery (Recovery Academy Australia 2012). This has resulted in a state-level reform road map (Victorian Department of Health 2012) where the principles of recovery are prominent and will drive the restructuring of the treatment system.

66.3 What Does "Recovery" Mean?

The term "recovery" has been ubiquitous in the substance abuse field for half a century if not longer but, until recently, had remained undefined. Researchers typically operationalized the term in studies by measuring short-term abstinence (typically a year or less), some from a single substance (e.g., alcohol) and others from all substances (for a discussion, see Laudet 2007). The field began to delve into the meaning of "recovery" in 2005 when the Center for Substance Abuse Treatment (CSAT), a division of the Substance Abuse and Mental Health Services Administration (SAMHSA), convened a panel of experts representing a number of key stakeholder

groups (Center for Substance Abuse Treatment 2006). The following year, the Betty Ford Center convened a smaller panel of experts and stakeholders that published the first consensus definition of "recovery" as "voluntarily maintained lifestyle composed characterized by sobriety, personal health, and citizenship" (Belleau et al. 2007, p. 221). Other definitions have since been formulated, but all share the premise that SUD recovery goes well beyond the reduction of/desistance from substance use and extends to improved functioning in key life areas typically impaired but active use. Stated differently, one can regard recovery as currently conceptualized as non-problematic substance use (or total abstinence) *plus* improved functioning in such areas as physical and mental health, employment, economic, family, and social life, to name only a few. Central to this new model is that recovery is a dynamic and individual process whereby the combination of factors defining recovery is individually determined and may well change over time as recovery progresses.

66.4 What Does Adopting a Recovery Orientation Mean for Addiction Treatment Services?

Broadly stated, the two elements of the paradigmatic shift discussed above mean that SUD services need to be expanded in time, in philosophy, and in scope. In terms of time, SUDs have thus far been addressed using intensive, short-term episodes of professionally delivered services in in- and/or outpatient settings. While the effectiveness of treatment has received support (Waldron and Turner 2008; Weisner et al. 2003b), the rate of return to active use following treatment, even among those who had achieved abstinence (the goal of treatment in the United States), is high (Dennis et al. 2005; Laudet et al. 2007; McLellan et al. 2005a). This typically leads to treatment reentry (be it in the community or in jail settings) as well as to numerous costs to the individual, to his/her community, and to society. On the other hand, there is evidence that participation in ongoing recovery support – typically 12-step fellowship meetings such as Alcoholics Anonymous, often the only available community-based recovery support resource until very recently but also less structured forms of community engagement and activities – is associated with decreased rates of return to active substance use (Fiorentine and Hillhouse 2000; Kyrouz et al. 2002; Laudet et al. 2007; Tonigan 2008) and with utilization of costly services (Humphreys and Moos 2001, 1996). Taken in a broader context, the empirically demonstrated usefulness of mutual aid recovery support groups emphasizes the importance of peer and most notably the critical role on ongoing support to sustaining recovery (see later section).

In terms of scope, a recovery orientation requires the provision of comprehensive services designed to address needs in all life areas that are typically impaired during active addiction and where improvements are considered an inherent part of recovery – e.g., physical and mental health, employment, economic, family, and social life (see preceding section). Services addressing these issues have thus far often been referred to as "ancillary" in status or "aftercare" in the timing of delivery in spite of their importance to clients, and their evidences impact on the transition to

stable recovery (Laudet et al. 2009; Laudet and White 2010). One study illustrating the importance of non-addiction-related services to treatment clients interviewed individuals who had left treatment before completion – in that study, 60 % of the cohort has left before completion, a finding on par with the national average (Substance Abuse and Mental Health Services Administration Office of Applied Studies Treatment Episode Data Set (TEDS) 2005, 2008). We asked clients why they left the program and whether they felt there was anything the program could have done differently to keep them engaged in services longer (Laudet et al. 2009). Answers fell into one of three broad categories, none of which mentioned addiction treatment services: need for social services (54.2 % – job training, help with housing, childcare, stable housing), need for more supportive staff (25.8 % – e.g., encouraging, trusting, and caring), and need for greater schedule flexibility to accommodate other responsibilities, including work (20 %). These findings are consistent with that of another study we conducted examining current challenges and life priorities in a sample of 356 community-based persons in abstinent recovery from severe polysubstance dependence (Laudet and White 2010). Participants' responses were examined as a function of how long they had been abstinent: under 6 months (28 %), 6–18 months (26 %), 18–36 months (20 %), and over 3 years (26 %). Across these stages, working on one's recovery (e.g., staying sober, "making recovery a priority") was consistently cited as the top priority (cited by 34–49 % across stages); notably, employment was the second most frequently mentioned priority at all stages, cited by the same percentage of persons abstinent over 3 years as working on one's recovery (34.1 % each). Taken together, findings from these studies underline the importance of services designed to foster improvement in non-addiction functioning among both individuals in treatment and those at various stages of the recovery process.

The comprehensive recovery-oriented service model is significantly different from the currently prevalent model where services focus, by necessity, on substance use-related issues and are delivered by trained addiction professionals. Note that delivering a comprehensive recovery-promoting approach does not require that all services be delivered in a single setting, nor does it signify the approaching disappearance of "addiction treatment" as practiced today. In the next section, we summarize prevalent models of recovery support services.

66.5 What Do Recovery-Oriented Addiction Services Systems Look Like?

As clinicians and researchers have come to recognize the chronic nature of SUD, they have developed and evaluated a growing menu of interventions designed to help clients sustain and build on their treatment gains – i.e., relapse prevention. Perhaps the most prevalent form of aftercare consists of *a stepped down course of services typically following intensive inpatient* or residential treatment (McKay 2001, 2009; McKay et al. 2009); in spite of its established existence and intuitive appeal, few clients access these resources and the evidence for the effectiveness of the approach

remains limited (Godley et al. 2007; McKay 2001). In the past decade, clinicians have also started to capitalize on health technology such as telephone-based continuing care (McKay et al. 2005), and several large treatment agencies are developing proprietary web-based online recovery maintenance and support programs for clients to use after they leave service; one example is Hazelden's MORE.[1]

66.6 Recovery-Oriented Systems of Care

In the United States, the shift to a recovery orientation in SUD services has been primarily spearheaded by the Substance Abuse and Mental Health Services Administration (SAMHSA). SAMHSA is advancing the Recovery-Oriented Systems of Care (ROSC) model that constitutes an organizing framework for recovery support services. A key premise underlying recovery supports is that addiction is typically a chronic rather than acute condition. While a chronic condition cannot be "cured," the symptoms can be arrested and the condition managed. The need for this new model was perhaps stated most explicitly by Dr. Clark, a SAMHSA official: "Recovery is more than abstinence from alcohol and drugs; it's about building a full, meaningful, and productive life in the community. Our treatment systems must reflect and help people achieve this broader understanding of recovery" (Clark 2008b, p. 2). As described in SAMHSA materials,[2] ROSC's goals are to intervene early with individuals with SUDs, to support sustained SUD recovery, and to improve the health and wellness of SUD-affected individuals and families. Consistent with the multidimensional and developmental nature of recovery discussed earlier in this chapter, the ROSC model proposes a multisystem, person-centered continuum of care in which a comprehensive menu of coordinated services and supports is tailored to individuals' recovery stage, needs, and chosen recovery pathway (Clark 2008a, b). Services and supports are provided in a comprehensive array of recovery-related domains including education and job training, housing, childcare, transportation to treatment and work, case management, spiritual support, as well as SUD-focused services – e.g., relapse prevention, recovery support, SUD education for family members, peer-to-peer services and coaching, self-help, and support groups (Kaplan 2008; Sheedy and Whitter 2009).

Services are intended to address the multitude of life areas adversely affected by active substance use and to respond to clients' changing needs across their life span. ROSC is responsive to calls from the Institute of Medicine and leading addiction researchers for a shift in SUD treatment from the acute care model to one more akin to the model used in other chronic conditions (Humphreys and Tucker 2002; Institute of Medicine 2005; McLellan et al. 2000; White et al. 2005a). From a systems perspective, this means that the case management and care coordination function of services is conferred a more prominent role in treatment design and delivery.

[1] http://www.hazelden.org/web/public/more_demo.page

[2] http://partnersforrecovery.samhsa.gov/rosc.html

Key principles guiding the recovery orientation include primacy of participation; promoting access and engagement; ensuring continuity of care; employing strength-based assessment; offering individualized recovery planning; functioning as a recovery guide; community mapping, development, and inclusion; and identifying and addressing barriers to recovery (Kirk 2008, 2010; Tondora and Davidson 2006).

Implementing ROSC nationwide in the United States will require transformative changes in agencies that address SUD directly as well as within those serving the population through other avenues (e.g., mental health and social service agencies). This has implications for the training and evaluation of staff and service managers and those responsible for commissioning and evaluating treatment services. The Affordable Care Act's expansion of Medicaid and the creation of health insurance exchanges give states added resources to make these changes. At this writing, ROSC is gradually taking hold as more states and cities are implementing components of the model (Evans 2007; Kaplan 2008; Kirk 2008). Still, the ROSC model is still in its infancy at the level of field implementation and, at this writing, has not been formally evaluated. There is, however, emerging evidence supporting its potential usefulness. Statewide data from Connecticut – the first to begin implementing a true ROSC in 1999 (Kirk 2010) – provide early support for the effectiveness and cost-effectiveness of the approach: this includes a 24 % decrease in expenses, 25 % decrease in annual cost per client, 46 % increase in number of people served statewide, 62 % decrease of acute care, 40 % increase in outpatient care, and 14 % lower cost with recovery support. Internationally, untested belief that a recovery-oriented approach is prohibitively expensive has been a significant barrier to implementation and one that needs to be tested with adequate effectiveness and cost-effectiveness evaluations and health economic research.

66.7 Individual Recovery Support Services Elements

In addition to the emerging system-level recovery orientation embodied by ROSC, the field is also witnessing the development of a growing menu of recovery support services (RSS) described in a number of recent articles and monographs that also review the emerging science supporting the approach (Kaplan 2008; Laudet and Humphreys 2013; Sheedy and Whitter 2009; White 2008, 2009). Unlike professionally delivered aftercare (see earlier), peer-based RSS are not solely conceptualized to be delivered after treatment but can also be provided in addition to or even in lieu of professional services. This is important as there are a number of barriers to SUD treatment that include wait lists, finances, stigma, and ambivalence about seeking professional help (Appel et al. 2004; Cunningham et al. 1993; Laudet et al. 2009; Zemore et al. 2009).

At least two aspects of RSS are unique. First, RSS are often delivered by peers, individuals who have experiential knowledge (Borkman 1999) and work as volunteers or as paid service workers (Kaplan 2008) to assist others in initiating and maintaining recovery and enhancing their quality of life (White 2009).

Other healthcare fields have capitalized on peers to promote symptom management in the context of chronic conditions (e.g., asthma, cancer, psychiatric illness, and diabetes – Greenfield et al. 2008; Kyrouz et al. 2002). A randomized clinical trial using a prospective design with repeated measurements documented the effectiveness of adding a peer-based component to clinical treatment in reducing substance use (Rowe et al. 2007) among clients dually diagnosed with a mental health and a substance use disorder, and peers have also proven effective at designing and disseminating mutual help-related public service announcements to increase involvement in mutual aid/self-help groups for a range of chronic problems, including SUD (Humphreys et al. 2004). The use of peers is intuitively appealing and empirically demonstrated to be useful in the addiction field as well. Research has shown that social support, particularly from other individuals in recovery, predicts successful substance use outcomes (Humphreys et al. 1999, 1997; Weisner et al. 2003a). Many individuals in recovery report that being in the company of peers is helpful (Granfield and Cloud 2001; Laudet et al. 2002; Margolis et al. 2000; Nealon-Woods et al. 1995). In Glasgow, Scotland, one study found that the two strongest predictors of positive quality of life in recovery were spending time with other people in recovery and engagement in meaningful activities – including working, training, volunteering, and involvement in community groups (Best et al. 2011).

The second unique aspect of peer-based RSS is that they can be delivered in a broad range of community-based settings – e.g., recovery community centers, faith-based institutions, jails and prisons, health and social service centers, and addiction and mental health treatment agencies (Faces and Voices of Recovery 2010). This is important not only because it increases the accessibility of recovery support literally (i.e., to persons who may not have the means of transportation to go to a treatment program) but also more figuratively by removing some of the stigma and ambivalence that are sometimes attached to "seeking help" in a traditional healthcare or SUD treatment setting.

One type of peer-based recovery support service that is increasingly being implemented in the United States is peer recovery coaching: a peer mentors the individual seeking recovery (e.g., assists in setting recovery goals and a recovery plan, serves as role model in recovery). This aims to help the individual connect to recovery-supportive resources needed to restructure life (e.g., professional/nonprofessional services including housing and employment) and serving as an advocate and liaison to formal and informal community supports, resources, and recovery-supporting activities. While no formal evaluation of peer recovery coaching has been conducted to date, a clinical trial of an integrated case management including using peer coaches to help integrate SUD treatment and child welfare services for parents in substance-involved families enhanced access to treatment and resulted in increased family reunification rates compared to standard care (Ryan et al. 2006). Moreover, reports compiled in the context of broader recovery-oriented efforts have provided emerging evidence for the benefit of peer coaching (Mangrum 2008).

There are a handful of other models of peer-based recovery support that we only briefly describe here as they are more fully discussed in a recent review

article (A. Laudet and Humphreys 2013). One model is the sober residence, a home that offers mutual help-oriented, financially self-sustaining, self-governed, democratic communal-living environments where individuals in recovery can reside for as long as they choose after inpatient treatment or incarceration, during outpatient treatment or as an alternative to treatment (Polcin 2009). The most prevalent model of sober residences is Oxford House (OH) with 1,300 houses in the United States (Jason and Ferrari 2010). The benefits of the model in terms of substance use and related domains (e.g., employment, criminal involvement) have been extensively documented in prospective peer-reviewed studies across subpopulations (Alvarez et al. 2006; Jason et al. 2001, 2009; Majer et al. 2002, 2011; Millar et al. 2011), as has been its cost-effectiveness (Lo Sasso et al. 2012; Olson et al. 2006). Most recent and perhaps most innovative is the campus-based Collegiate Recovery Program (CRP) model that is emerging nationwide. The high prevalence of substance use on college campus can jeopardize recovery for young people at a time of their development where fitting in with peers is central to their identity; for some, that may lead to foregoing or postponing college in the absence of a readily available sober network (Baker and Harris 2010; Botzet et al. 2007; Harris et al. 2008; Laitman and Lederman 2007; Smock et al. 2011; U.S. Department of Education Higher Education Center for Alcohol and Other Drug Abuse and Violence Prevention 2010; Woodford 2001). The CRC developed to meet the needs of college students with a history of SUD who have successfully remitted from the disorder and seek to pursue educational goals. Central elements of the CRC model include a peer-driven approach informed by 12-step tenets and services such as drug-free housing, on-site peer support, and counseling provided by a small staff, as well as opportunities for sober recreational activities, relapse prevention, and life skills workshops. Little documentation is currently available about specific CRC services across programs, but it is believed that the breadth of service varies (Bell et al. 2009). Common to all are on-site 12-step and other recovery support meetings, a campus-based location where students can meet and spend time with sober peers; some offer sober housing and peer academic support. All function with minimal professional staff as the emphasis is clearly peer driven. The model seems consistent with the continuing care paradigm within a "recovery management" system that experts recommend (Godley et al. 2002). CRCs are also responsive to calls for appropriate campus-based infrastructure to support recovering students (Misch 2009), with recent shifts in drug (Office of National Drug Control Policy 2010) and with the US Department of Education's goal of ensuring a continuity of care from high school to college to postgraduation (Dickard et al. 2011). The model is growing in popularity nationwide: in the past decade, growing concerns about substance use on campus and federal agencies' focus on building a community-based continuum of care system for youths have fueled a fivefold increase in the number of CRPs, from four in 2000 to 32 in 19 states today. No formal evaluation has been conducted yet, but site-specific reports document

encouraging outcomes – low relapse rates, above school average GPAs, graduation rates, and perceived helpfulness (Baker et al. 2011; Bell et al. 2009; Cleveland et al. 2007; Harris et al. 2008). The first author is currently conducting an NIH-funded survey of all CRC programs and student participants nationwide to learn more about the breadth of services offered and the characteristics and needs of students served; that knowledge will inform a subsequent large-scale evaluation of the model. In the same vein as CRCs though professionally rather than peer delivered are recovery high schools (Moberg and Finch 2008) that typically function as charter schools in a public school system and serve students who recently left SUD treatment. This model is currently undergoing systematic evaluation.

The three initiatives discussed above – around education, housing, and peer activities – are all consistent with three core tenets of recovery-oriented services: a care coordination across a range of service sectors requiring case management skills and "outward-looking" specialist treatment services, an increased role for peers and a recognition of the validity of "expertise by experience," and a continuity of care model that acknowledges the need for integrating acute services with those targeting longer-term changes in well-being and social integration. This grassroots or "bottom-up" approach represents a drastic departure from the current SUD service model. Moreover and importantly, it is accessible to individuals who have reservations about the mutual aid movement (12 steps in particular) and is consistent with an asset-based community development model (Kretzmann 1993) and with the public health model to addictions that is gathering momentum in the United Kingdom and elsewhere in Europe.

Overall, a growing menu of professionally and peer-delivered recovery support services is being developed and implemented, with the professionally driven efforts being spearheaded (in the United States) by federal funding agencies, principally SAMHSA. None of the peer-driven strategies have been formally evaluated though state-level data report encouraging outcomes. These findings are of course preliminary; the approaches need to be systematically evaluated, and the stability of the documented improvements over time remains to be determined.

66.8 What Can Medical Professionals Do to Promote Recovery Among Substance-Using Patients?

Given the prevalence of substance use disorders and how frequently medical and substance use disorders co-occur, medical professionals routinely come into contact with patients who are or were abusers of/dependent drugs and/or alcohol. This section briefly outlines suggestions for medical professionals to promote the initiation and maintenance of recovery from substance use disorders.

Addressing active substance use in primary care as Screening, Brief Intervention, and Referral to Treatment (SBIRT)[3] is increasingly being implemented and evaluated. The rationale behind SBIRT is simple yet effective: identifying (screening) a substance use problem early reduces the risk that it will progress to clinical levels (in this case, chronic SUD); this secondary prevention approach (preventing disease progression) is accomplished either through a brief intervention delivered by the professional conducting the screening, immediately following detection of a problem, or through referral to specialty care (i.e., SUD treatment) when the severity of the identify problem warrants it. There is a growing body of evidence for the effectiveness of SBIRT across populations (adults, youths, veterans) and across settings – e.g., primary care and emergency departments (Agerwala and McCance-Katz 2012; Gonzales et al. 2012; Gryczynski et al. 2011; Lotfipour et al. 2013; Madras et al. 2009; Mitchell et al. 2013; Murphy et al. 2013; Young et al. 2012). The effectiveness of brief intervention has long been established, with the largest trial being conducted by the World Health Organization (WHO): 1,661 heavy drinkers in 8 countries were randomly assigned to a control condition (no intervention) or to one of two forms of brief intervention to reduce drinking. At a 6-month follow-up, participants receiving either of the two brief interventions showed significant reductions in drinking outcomes compared with the control group (WHO Brief Intervention Study Group 1996). Implementing SBIRT in primary care is especially critical in view of the fact that studies of SUD treatment clients show that two decade or more pass between first and last uses (Dennis et al. 2005). Fewer than 10 % of individuals needing SUD treatment seek it in a given year (Kessler et al. 1996; Wang et al. 2005), about a third in their lifetime (Compton et al. 2007; Hasin et al. 2007). Therefore, it is critical to capitalize on opportunities to address substance use problems early, and primary care settings (as well as emergency departments) represent very promising venues to achieve that goal. Addressing substance use in primary care is also essential because substance use can complicate the course of other diseases and jeopardize adherence to and outcome of treatment (Braithwaite et al. 2007; Oyugi et al. 2007; Watson et al. 2007). In addition to promoting the initiation of recovery through such strategies as SBIRT, healthcare professionals are also in a position to help support recovery *maintenance*. Continued screening for substance use in patients with former SUD is desirable to detect any relapse early – as is currently routinely done for mental health problems during office visits. Moreover, active addiction has numerous negative consequences for many major organs and systems (e.g., liver, heart, and lungs) as well as the potential for undiagnosed infectious disease (e.g., HIV/AIDS and Hep C); years of active addiction often result in neglected self-care, increasing the odds that any developing medical condition progresses unaddressed. Therefore, because individuals with an SUD history have lower access to health services (Samet et al. 2007), they may be at enhanced risk for developing chronic

[3] http://www.samhsa.gov/prevention/sbirt/SBIRTwhitepaper.pdf

conditions; it is important that healthcare professionals educate themselves about the consequences of active addiction and screen patients with a history of SUD for conditions frequently associated with an addiction history. Studies have documented the high rate of co-occurring chronic medical (and mental health) conditions among persons with a history of SUD, both of which complicate also the attainment of recovery outcomes such as seeking employment A cross-national trial of brief interventions (Laudet 2012). Overall, the evidence suggests that substance use (be it active or past) interacts dynamically with physical health, enhancing the need for healthcare professionals to engage patients in an honest, nonjudgmental dialogue about their current and past substance use.

Finally, though a full discussion is beyond the scope of this chapter, the treatment of acute and chronic pain for patients in recovery from an SUD is a growing area of research and of practice for healthcare professionals, discussed in details in several recent book chapters and articles (Brown et al. 2012; Cruciani et al. 2008; Miotto et al. 2012; Portenoy et al. 2005).

66.9 Conclusion

The emerging recovery orientation builds on a growing addiction science and an evidence base that shows the effectiveness of a range of treatment interventions. It also represents a paradigmatic shift in the way SUD recovery is conceptualized and how recovery services are delivered both at the individual and at the systemic level. Recovery is an organizing concept that promotes empowerment and choice within a change model based on a chronic disorder with unpredictable rates of relapse necessitating a service model that integrates acute interventions with holistic, comprehensive care coordination and community engagement. Recovery services approaches are consistent with the needs of the recovery community as documented in a handful of studies summarized here and have a burgeoning evidence base around peer support, around recovery housing, and around long-term transitions to training and employment. Healthcare professionals in all sectors should become familiar with the breadth and growing availability of recovery services and supports in their communities as these resources supplement and for some may replace traditional SUD treatment. Doing so will allow providers to have a larger menu of options to discuss with and offer patients, with the ultimate goal of reducing the duration and impact of active substance use and SUD, and giving patients the resources necessary to improve their overall health and functioning.

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Applying Technology to the Assessment, Prevention, Treatment, and Recovery Support of Substance Use Disorders

67

Lisa A. Marsch and Sarah Lord

Contents

Abstract

This chapter summarizes the growing body of research demonstrating that science-based information and communication technologies (e.g., delivered via the web and/or on mobile devices) offer great promise in targeting the full spectrum of substance use disorders, ranging from assessment and prevention to treatment and recovery support. This chapter provides a summary of the growing scientific literature showing that these tools (when they are well developed and in close collaboration with the target audience) may be engaging to the target

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audience and effective in a number of models of deployment. The chapter additionally reviews the potential public health impact of this approach when integrated into various models of care targeting substance use disorders. Overall, these tools offer great promise for changing models of service delivery targeting substance use disorders (as well as other areas of behavioral health) to increase quality and reach of care while containing costs in a wide array of settings and countries. Finally, the chapter reviews best practice models for implementation of technology-based care approaches and research needs and opportunities.

67.1 Introduction

67.1.1 The Promise of Technology

A growing body of research suggests that science-based information and communication technologies (e.g., delivered via the web and/or on mobile devices) offer great promise in targeting the full spectrum of substance use disorders, ranging from assessment and prevention to treatment and recovery support. These tools may be accessed in a wide array of settings, such as when individuals move about their daily lives, in the privacy of their own homes, in specialty addiction treatment programs, or in primary care settings. And they can enable a broad reach of effective assessment and intervention tools that can be accessed on demand and at low cost.

In the assessment arena, these tools may help individuals and their providers better understand if they meet the criteria for problematic substance use and/or understand how their substance use relates to normative data from a broader community (e.g., persons of the same gender and in the same generation). These tools may also help individuals monitor their own substance use and better understand patterns in their use (e.g., how often they use in a given period of time, how their use may be related to other aspects of their lives such as mood, exposure to specific peer groups, and/or specific settings). Additionally, using technology-based assessment tools generally leads to more accurate reporting of sensitive behavior (e.g., risky substance use, risky sexual behavior) relative to more traditional, person-delivered assessment.

Technology-based applications in the area of substance abuse prevention may be designed to teach protective factors and reduce risk factors for substance use and other risk behavior among children and adolescents (e.g., via interactive multimedia games). They may also focus on the prevention of substance-related harms (e.g., in college/young adult populations, among an HIV-positive community).

The application of technology to treatment may include an array of behavior therapy interventions, including tools for interactive skills training, self-management, and goal setting/tracking to foster change in problematic substance use and achieve functional outcomes (e.g., get a degree, get a job, improve an interpersonal relationship, be a better parent). Additionally, behavioral self-monitoring/assessment tools may be linked to interventions and can be designed

to trigger personalized interventions depending on an individual's needs and preferences (e.g., when one may be at risk for relapse). The advancement of mobile and web-based technologies now allows for ongoing, real-time recovery support beyond the boundaries of traditional recovery models.

Technology also allows for tailoring of user experiences based on a variety of individual factors (e.g., level of severity of use, co-occurring mental health problems). With technology, interventions can also be tailored over time (e.g., adaptive interventions that can change based on progress a person is making in reaching intended goals).

67.2 Applications of Technology

67.2.1 The Scientific Support

A growing scientific literature is showing that these tools (when they are well developed and in close collaboration with the target audience) may be engaging to the target audience and effective in a number of models of deployment. When provided as an adjunct to a traditional model of care, these tools may enhance the quality, reach, and outcomes of care (e.g., enhance outcomes in substance abuse treatment and/or HIV prevention) (Carroll et al. 2008; Marsch et al. 2011). When compared to science-based interventions delivered by highly trained educators/clinicians, some data suggest these tools may be of comparable effectiveness (Budney et al. 2011; Kay-Lambkin et al. 2009). These findings underscore the scope of effects that can be achieved with a technology-based model of intervention delivery. Additionally, technology-based tools may enhance treatment outcomes and allow for greater capacity for service delivery if they are provided in a model where they replace a portion of traditional models of care (e.g., a substance abuse treatment program can care for more clients if a portion of intervention delivery is provided via a technology-based system of care). Further, a number of scientific studies have supported the effectiveness of a direct-to-consumer model. There is additionally evidence that these tools may be cost-effective (Olmstead et al. 2010).

[For a comprehensive review of the state of scientific research developing and evaluating technology-based therapeutic tools targeting behavioral health, refer to ▶ Chap. 60, "Computerized Therapies: Towards an Addiction Treatment Technology Test" by Budney and colleagues in this same volume].

67.2.2 The Opportunity for Public Health Impact

As highlighted from the research described above, technology-based assessment, prevention, and behavior change intervention tools may be clinically useful when integrated into various models of care targeting substance use disorders. Overall, these tools offer great promise for changing models of service delivery targeting substance use disorders (as well as other areas of behavioral health) to increase quality and reach of care while containing costs.

The utility of technology-based therapeutic tools for substance use and other behavioral health care may become even more pronounced in the USA, given evolving models of health care (under the Affordable Care Act of 2010) which will expand federal insurance coverage for the first time to an estimated 32 million individuals who are currently uninsured. It is expected that many of the uninsured who will receive insurance for the first time are individuals that are poor and unemployed, with disproportionately high mental health and substance use problems (Substance Abuse and Mental Health Services Administration 2010). Technology may be useful as part of an integrated model of care as the current health-care workforce seeks to embrace this large influx of new clients.

Technology-based therapeutic tools may also be useful to the majority of persons with substance use disorders who are not engaged in traditional models of care for their problematic substance use. For example, in the USA, about one in ten Americans are estimated to be diagnosable with one or more types of substance use disorders, and the majority of these individuals (about 90 %) are not engaged in substance abuse treatment. Technology offers a mechanism for providing access to effective interventions for these persons who are not in care and may, in some cases, serve as a conduit to more formal models of care for substance use.

Substance use and mental health disorders are also highly prevalent among persons with chronic physical health conditions and greatly reduce the effective management of chronic illness. Co-occurring chronic illness and behavioral health problems have been associated with lower quality of life, poorer response to treatment, worse medical and psychiatric outcomes, higher mortality, and higher costs of care (Cimpean and Drake 2011). Leveraging technology in the integration of behavioral health and physical health disorders offers great promise in overall health-care management.

67.2.3 Opportunities for Developing Countries

The potential for emerging technologies, particularly mobile technologies, to change the face of health research and health-care delivery in developing countries is enormous given the high penetration of these technologies in these countries. In addition, many factors constrain health system performance in developing countries. Infrastructure is limited, and hospital resources are concentrated in urban areas. Incidence of disease and its impact on people's livelihoods and economic productivity is high. In many areas, there is also a severe shortage of health-care workers (in some areas one to every 250,000 patients) (Scheffler et al. 2009), and workers are difficult to recruit and retain, especially in rural areas. Supervisory and care management systems are often lacking or weak.

The burgeoning growth of cellular infrastructure in developing countries has considerable prospects for reaching and following individuals who were previously unreachable. Technology-based therapeutic tools can reach broad population bases with targeted care, including treatment, augments to clinical care, and self-management tools. For example, there is growing evidence that automated

medication and treatment reminders improve medication adherence and health among individuals living with HIV (Lester et al. 2009). Mobile technologies can also broaden access to education and training of health-care professionals via easily accessible online learning. The resource sharing capacities of cloud computing can be harnessed to improve health system management, workflow, and communication between providers in the service of care coordination (Kahn et al. 2010).

67.2.4 Research Needs and Opportunities

The rapid emergence of innovative technologies such as wireless and mobile devices has introduced exciting opportunities for researchers and providers alike. We are now in a reality in which wearable sensors that measure physiological metrics such as heart rate, skin conductance, and accelerometry can be feasibly worn naturalistically in daily living. Current technologies allow us to harness the existing sensor systems of mobile devices, such as global positioning systems (GPS), accelerometry, and microphones to collect valuable information about individuals' location, motion, and voice. These physiological, geographic, movement, and sound metrics can now be readily coupled with real-time mobile ecological momentary assessment surveys to produce continuous streams of data on an individual's physiology and psychology (attitudes, symptoms, cognitions, and emotions), with the potential to yield new insights into the factors that lead to substance use and mental illness. The potential to use these convergent sources of data to identify precursor signatures of substance use behaviors will ultimately allow for delivery of in-the-moment interventions when individuals need it the most. Advances in mobile health, or mHealth, have the potential to change when, where, and how health care is provided.

Yet, while the implications of mHealth for delivery of care for substance use and co-occurring disorders are tremendous, the development of technologies, such as wearable and physical sensors and the myriad of health "apps," has far outpaced the science needed to understand their benefits, risks, and impact on health outcomes. The empirical support for emerging technologies, such as sensors, as potential tools for care of substance use disorders and other behavioral health issues is in its infancy. There is much basic research to be done to better understand how, and if, these emergent technologies can feasibly and effectively be harnessed to impact substance use disorders and associated behaviors.

67.2.5 Best Practice Models for Implementation of Technology-Based Care Approaches

Despite a growing evidence base and enthusiasm for the potential of technology-based therapeutic tools to broaden and enhance care delivery, adoption has been slow. There is much research to be done to understand best practice strategies for disseminating evidence-based technologies to consumers and integrating

these technology-based approaches into systems of care. One main advantage of technology-based care approaches is the ability to reach broad consumer populations across time and setting. As such, it is critically important to understand individual and organizational characteristics associated with readiness to implement technology-based approaches to care delivery across diverse settings, including direct-to-consumer venues, schools and other community-based organizations, criminal justice, and health-care organizations.

Existing models of organizational readiness to adopt innovations, grounded in the diffusion of innovations theoretical framework (Rogers 1995), can guide dissemination and implementation research on adoption of technology-based therapeutic approaches. Extant research has identified a number of factors that influence the adoption process, including general organizational perceived need for change and a climate marked by clarity of mission, stable and supportive leadership, staff cohesion and cooperation, open communication, and adaptability and openness for embracing innovations and change (Greenhalgh et al. 2004; Rogers 1995). There is solid evidence supporting the importance of organizational readiness for promoting successful implementation and sustained adoption of treatment innovations within behavioral health-care settings, but little is known about the readiness of these care settings to implement technology-based therapeutic approaches. In a recent survey study of administrators and clinical directors at community behavioral health-care settings in the USA, organization readiness to use technology-based initiatives was associated with both internal (e.g., clients, staff, supervisors/managers) and external (e.g., funding sources, reimbursement policies) pressures for change, perceived readiness to meet demands of health-care reform, current use of technology in some capacity in the care setting, and low concerns about privacy with the use of technology (Lord et al. 2013).

Future implementation science research focused on technology-delivery therapeutic tools for substance use and co-occurring behavioral health issues could include implementation demonstration trials that focus on optimization of implementation outcomes as a necessary first step in producing better client outcomes (Proctor et al. 2011). These implementation outcomes include *end-user acceptance and satisfaction* with the technology (i.e., how did stakeholders like the technology), *feasibility* of implementation with specific stakeholders (i.e., did stakeholders use the technology as intended), *fidelity* of implementation (i.e., did stakeholders use the technology as intended), *penetration* of the technology among stakeholders (i.e., what proportion of stakeholders used the technology, for how often, and what components), *likelihood of adoption* (i.e., would stakeholders use the technology in the future), and *cost* of implementation (i.e., how did use of technology impact staff time/resources/costs?). Such implementation research should also include assessment of characteristics of the intervention, external and internal organization influences, individual stakeholder groups, and the implementation process itself that are associated with positive implementation outcomes (Damschroder et al. 2009).

While addressing implementation challenges associated with the use of technology-based therapeutic solutions, researchers should aim to identify barriers and solutions associated with issues of privacy, confidentiality, regulatory control,

human subjects' protection, and accessibility (e.g., interoperability among carriers) with the use of these tools. From a practical perspective, effective dissemination and implementation of technology-based care delivery approaches can benefit from effective marketing strategies to promote buy-in of leadership and key opinion leaders through emphasis on value of the technology for each stakeholder group, accessible and comprehensive training procedures for all stakeholders to foster self-efficacy and motivation to use the technology, and ongoing technical assistance to support integration of the technology solution within an organization culture.

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Residential Treatment

68

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Contents

68.1 Introduction

Attempts to solve alcohol-related problems have been with us for millennia. Five-thousand-year-old Egyptian records describe the care of those "mad from wine and beer" (White) in private homes of the time. Later, the Greeks and the

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Romans were known to recommend both public and private asylums for those addicted to alcohol. In the early nineteenth century in the United States, Dr. Benjamin Rush (1746–1813) is often credited with one of the first proposals to treat the disease of intemperance with medical care and residential treatment. He has been called the "father of American psychiatry" and wrote what became the first American medical textbook. Other American physicians followed suit with similar recommendations in the mid-nineteenth century including Eli Todd, Samuel Woodward, and Joseph Turner.

Rush's interest in chemical dependency issues seems to have arisen from his own family experience. His father's alcoholic drinking contributed to his parents' divorce. His mother was later remarried to a distiller who abused her. On a professional level as physician-general of the Continental Army, Rush was struck by the problems created by inebriation in the Army. In 1777 his essay condemning the use of distilled liquor was distributed to all soldiers. In his 1782 newspaper article "Against spirituous liquors," Rush recommended that farmers stop providing laborers with daily allocations of liquor. In 1784 he published a 36-page pamphlet, An Enquiry into the Effects of Spirituous Liquors on the Body, and Their Influence Upon the Happiness of Society.

Rush first promoted the chronicity and progression of alcoholism as a medical ailment, opening the door to addiction to alcohol as a treatable condition. He attributed this progression to a "disease of will" and recognized the frequent familial expression of alcoholism. Although his ideas were not readily accepted by the general public at the time, his writings and teaching of scores of young physicians at the Philadelphia School of Medicine laid the foundations for the temperance movement which followed. Working independently, Rush's international contemporary in England, Dr. Thomas Trotter, wrote, "Essay, Medical, Philosophical and Chemical, on Drunkenness," also attributing to alcoholism the status of a medical illness. The "disease concept" of alcoholism as a medical malady was born.

68.2 Residential Programs

68.2.1 Beginnings of Inpatient Residential Treatment

Prior to the development of specialized alcohol and addiction treatment facilities, those suffering from these ailments often found their way to jails, charitable homes, workhouses, and lunatic asylums. None particularly welcomed the alcoholic or addict and none provided specific treatment for their rehabilitation or cure. Lacking the availability of treatment, many so afflicted simply hid their addictions throughout their entire lives.

Rush was fully cognizant of these challenges in treating alcoholism, so in 1810 he recommended the establishment of a "Sober House" for the confinement and rehabilitation of confirmed alcoholics. Confinement would be determined by "evidence of drunkenness, neglect of business, and ill-treatment of family members" (White). Religious and moral instruction would constitute treatment in this setting

and a judicially appointed committee determined discharge following adequate rehabilitation. As hospitals were scarce at the time and drunkards were viewed as morally ineligible for admission, along with unwed mothers and those suffering from venereal disease, "Sober Houses" may have seemed like a reasonable choice.

Alcohol-related problems also led to the birth of a series of personal recovery movements in the United States in the 1800s. The Washingtonian movement is perhaps the most well known but others included the Sons of Temperance, Good Templars, Good Samaritans, Osgood's Reformed Drinkers Club, Reynold's Red Ribbon Reform Club, Francis Murphy's Blue Ribbon Reform Club, Business Men's Moderation Society, and many others. These involved thousands to hundreds of thousands of reformed alcoholics and supporters, but all seemed to follow the same course of widespread appeal and growth followed by eventual demise. However, in aggregate they laid the groundwork for the rise of residential inebriate homes and asylums which was to follow.

In 1840, R. Grinrod proposed the establishment of inebriate asylums:

> Let the experiment be fairly tried; let an institution be founded; let the means of cure be provided; let the principles on which it is to be founded be extensively promulgated and I doubt not, all intelligent people will be satisfied of its feasibility. . .. At the head of this institution place a physician of zeal, medical skill and enlarged benevolence; let the principle of total abstinence be rigorously adopted and enforced. . ..let the appropriate medication be afforded; let the mind be soothed. . ..let the certainty of success be clearly delineated to the mind of the sufferer. . .. Let good nutrition be enjoined while the prostration of strength and energy continue. . ..this course, rigorously adopted and pursued, will restore none out of ten in all cases. (White)

Finally, in the later nineteenth century specific institutions for the treatment of addiction began to spring up. By 1870 six such inebriate asylums were in operation. Their managers soon got together to create the American Association for the Cure of Inebriates. The association included 32 members by 1878 and more than 100 institution members by 1902. Some of the first members included the Washingtonian Homes in Boston and Chicago, the New York State Inebriate Asylum, the Pennsylvania Sanitarium for Inebriates, the Kings County Inebriates' Home, and Walnut Lodge.

Many different monikers were attached to these sorts of institutions: inebriate asylums, inebriate homes, inebriate colonies, inebriate farms, lodging homes, reformatories, retreats, and sanitaria. Some provided room and board with minimal additional treatment. Others provided a sober place to stay while the residents attended temperance movement meetings. Some were established as medical facilities both privately and publically funded. Public funding, unfortunately, was often inconsistent. The goal of all of these institutions was the treatment of the alcohol dependence, although other chemical addictions were treated as well. Brooklyn Home for Habitues, founded by Dr. Jansen B. Mattison in 1891, was one of the first to focus exclusively on nonalcohol chemical addiction.

Medical treatment was often quite variable at this time with physicians caring for various medical problems and assisting in ambulatory detoxification. Some patients visited the physician 3–4 times a day while living at home or staying in a hotel.

More consistent treatment recommendations began to appear. The establishment of three tiers of continuum of care medical facilities was recommended by Dr. T.D. Crothers:

Level 1: Voluntary or involuntary residential stays of up to 1 year for acute cases of inebriety

Level 2: Residential stays of 1–3 years for chronic cases of inebriety

Level 3: Farm colonies or workhouses for incurable inebriates who could be forced to adhere to "military habits of life and work, and kept in the best conditions of forced healthy living" (Crothers 1893)

Generally, the first step of residential treatment was detoxification. Some recommended the "cold turkey" approach. Others supplemented this phase with a wide variety of medications including "whisky, beer, sherry, chloral hydrate, strychnine, atropine, coca, cannabis indica, atropine, hyoscyamus, belladonna, quinine, iron and placebos" (White). Physical restoration of the patient usually followed detoxification. Methods included treatment of medical issues, "rest, Turkish baths, massage, phototherapy (exposure to sunlight), electrotherapy (electrical stimulation), nourishing meals and vitamin supplements, high fluid intake, exercise, and lots of fresh air" (White). Spiritual or religious experience was thought to be necessary. Religious instruction, exposure to religious leaders, prayer, and Bible readings were all applied. Social support and exposure to similarly challenged individuals were believed to be helpful as well. Work and recreation were thought to be beneficial. Exposure to music, self-reflection, and moral suasion were all thought to benefit the recovering patient. Very little modern style counseling was provided but patients were encouraged to partake in acts of service. Finally various forms of aversion therapy were also applied.

Funding for the early addiction treatment programs came from a variety of sources: families, government grants, alcohol taxes, charitable donations, selling of patient-produced products, patient labor, and the patients themselves. Government funding was often sought but, as today, this source always carried the risk that approved funding streams could be diverted to other more socially desirable projects or needs. Even many of the privately funded programs often tried to provide a "charity" bed or two (White).

Some felt that the moral and practical responsibility to provide this care should that of the public sector. It was even suggested that funding be provided by a tax on the sale of alcoholic beverages.

On the basis of a report submitted by Dr. Charles Hewitt of the Minnesota Board of Health in 1873, the Minnesota legislature approved a law establishing a special saloon tax. The monies collected were slated for use in creating and operating a "treatment center for inebriates." Opposition at the time was able to derail this funding stream and funnel the money for general psychiatric care. But in 1907 the legislature created a two percent liquor tax with similar goals in mind. These funds were to be dedicated to the treatment of inebriates and Willmar State Hospital was born. Funding dried up in 1920 and alcoholism treatment responsibilities reverted back to various psychiatric facilities for the next 30 years.

From the earliest days, conflicts arose between the administrators of the inebriate treatment institutions and the administrators of the psychiatric institutions. Inebriate patients were categorically excluded from the state psychiatric institutions. Where to place patients suffering from a combination of inebriety and psychiatric illness became a bone of contention.

Psychiatric asylums often admitted their inability to deal effectively with inebriates and even judged them contrary to the welfare of their psychiatric patients. In addition, there were conflicts inherent in using the psychiatric treatments of the time. Whisky and opium were liberally used as psychiatric medications at that time and drinking and drug problems were apparently not uncommon among the psychiatric hospitals' staff (Geller and Harris 1994).

As early as 1875, Dr. Henry Bowditch in Massachusetts began to advocate for patient-helpers in the inebriate home treatment model. In addition to those former patients who were required to "work off" the cost of their treatment, Dr. Bowditch believed that recovering inebriates who possessed the education and intelligence had a moral duty to help those less fortunate patients. Some contributed in the clinical setting and others in the administrative or maintenance areas. Paid jobs for these individuals soon evolved and at times the line between patient and paid staff was muddled.

Wives and family members were often viewed as a nuisance by treatment staff. All too often the patients' spouses either interfered with treatment or acceded to the patients' wishes and pulled them out of treatment prematurely. The results, of course, were inevitable. Aftercare was spotty or nonexistent by the standards of today. Following residential treatment, the patient was often placed in the home of nondrinking friends. Involvement with a religious or fraternal temperance organization was encouraged.

In 1870, the American Association for the Cure of Inebriates was founded in New York City by a group of physicians, lay people, and inebriate asylums. The American Association for the Study and Cure of Inebriety statement of principles and purpose included the following (Crothers 1893):

- Intemperance is a disease.
- It is curable in the same sense that other diseases are.
- Its primary cause is a constitutional susceptibility to the alcoholic impression.
- This constitutional tendency may be inherited or acquired.

The statement further recommended that scientifically based residential treatment replaces the penal approach in fashion at the time for the treatment of addiction. The association also lobbied for state financial support for residential treatment and for laws which would mandate residential treatment for those suffering from inebriety. They were concerned with the spread of quack addiction cures and sought stronger regulation of addiction treatment medications, physicians, and institutions. Not everyone agreed with this approach; some even recommended that those suffering from the "hereditary weakness" of alcoholism be allowed to die, thereby cleansing society forever of alcoholism (Crothers 1893).

During this period the idea of individualized treatment was further developed. Treatment philosophies fell within two broad arenas. Asylums viewed the goal of recovery as physical regeneration resulting from the scientific treatments provided. Washingtonian homes understood recovery as a moral regeneration resulting from healthy, courteous, and respectful environment. Many questions were posed, some perhaps still unanswered. Should treatment be physical or moral? Should facilities be large or small? Should coercion be used or should treatment be purely voluntary? Superimposed on all this was the question of length of stay. Hopeful cases were treated for 6 months or less while more advanced cases of addiction were thought to require a minimum of 1–5 years of treatment. Mandated treatment was experimented with in some areas but the public looked disparagingly at these practices due to the conflict of interest apparent in this model.

Residential treatment came to a conceptual fork in the road at the end of this period. The young specialty of psychiatry described addiction as a symptom of a subconscious emotional pathology. Another view evolved that substance abuse reflected a willful misbehavior which must be criminally punished to be corrected. However, more so than by any other criteria, it appears that patients were segregated by social class and financial means. Those with social standing and financial means were treated by psychiatrists in private sanitaria. Those who lacked these assets were more likely treated in publicly funded asylums or made their way into the criminal justice system. These nineteenth-century ideas survive today and still influence the treatment of addiction. Well-to-do prescription addicts with good medical insurance are often said to be "chronic pain patients" suffering from "pseudo addiction," while those without financial means are more likely to be punished for their addiction within the criminal justice system or redirected to publicly funded methadone maintenance programs.

68.2.2 Residential Treatment in the Early Twentieth Century

A number of addiction "cures" appeared in the nineteenth century, including the Neal Institutes, the Oppenheimer Institutes, the Empire Institutes, the Gatlin Institutes, the Hagey Cure, and the Leyfield Cure. Arguably the most well-known was Leslie Keeley's Double Chloride of Gold Cure. More than a half million alcoholics and addicts took the Keeley Cure between 1880 and 1920. The heart of the cure was four injections a day of Keeley's secret Double Chloride of Gold formulation. In addition to rest, nutrition, and psychological support, graduated reduced doses of opium were used to detoxify opium addicts. At its peak there were more than 100 Keeley Institutes and the Keeley Cure was used in other institutions and sent out by mail order as well. Aftercare support was provided by the Keeley League, initially called the Bi-Chloride of Gold Club, boasting 30,000 members and 370 chapters across the United States.

Controversies swirled about the Keeley Institute and many critics surfaced over the years. Among the many criticisms was that the injections contained no gold and

were, in fact, merely placebo concoctions designed to keep the patients in residential treatment for 4 weeks. Leslie Keeley went to his grave without ever revealing the secret formula for his highly touted cure. The Keeley empire began to decline with the death of Leslie Keeley in 1900 but continued in operation for many years thereafter. In the 1940s, Alcoholics Anonymous arranged a loose affiliation with Keeley, and AA meetings were sometimes organized at Keeley facilities. The last patients were admitted to the original Keeley facility in Dwight, Illinois, in 1966.

Notwithstanding the many critics of Dr. Keeley's concoctions and marketing techniques, the Keeley phenomenon did advance the evolution of addiction treatment in many positive ways. First, Dr. Keeley's aggressive marketing campaigns helped to educate the public about the disease nature of alcoholism and addiction and its potentially successful treatment. Second, through this public education process, the stigma of alcoholism and addiction was reduced. Third, regardless of the actual physiological effects of the Double Chloride of Gold concoction, many addiction recoveries were initiated through its use. Fourth, many of those were attracted to treatment by the public's awareness of the large number of successfully treated patients coming out of the Keeley Institutes. Fifth, while the focus of the Keeley Institutes was residential treatment, the widespread mutual help network established by the Keeley League bridged the gap between the Washingtonians and the inception of Alcoholics Anonymous in 1935. Sixth, the Keeley philosophy of hiring recovered alcoholics and addicts laid the groundwork for many of the treatment philosophies of today. Seventh, more recovered physicians were employed by the Keeley Institutes than by any treatment provider either before or since. Eighth, the Keeley philosophy promoted an enthusiasm for sobriety for recovering patients, replacing the pall of punishment seen in some institutions of the day. And lastly, many permanent recoveries resulted from the healing environment established and promoted by the Keeley system of medically supervised detoxification, mutual support among residential patients, graduated renewal of both emotional and physical health, and engagement of patients in early sobriety in the miracle and magic of recovery.

As the twentieth century drew near, optimism reigned among those who envisioned the upcoming widespread availability of residential treatment for addictive disorders. Unfortunately, political and economic forces of the day were not aligned with the enthusiasm of treatment center founders. A look at the early decades of the twentieth century revealed a dramatic decline in residential treatment in the United States. For example, the Southern California State Asylum was founded but was neither opened nor built. Others were opened briefly but soon closed or were used for other purposes. Even the institutions that remained open experienced a tenuous existence (White). Crothers noted that only 30 of the first 50 inebriate asylums remained open and that many of those remaining drifted from their scientific orientation.

The Scientific Temperance Federation studied prohibition's effect on residential treatment in 1922. Of the 275 residential treatment facilities identified prior to prohibition, they were able to collect information on only 184. Of those, only 51 were still open for business. Most had closed their doors or redefined their

mission due to lack of admissions. Their research revealed only 27 dedicated residential inebriate treatment facilities nationwide (Stoddard 1922).

Inebriate asylum	Facilities at peak	Facilities in 1922
Gatlin Institute	5	0
Neal Institute	62	2
Keeley Institute	100	12

Even those that remained open experienced a dramatic drop in admissions. For instance, between 1919 and 1921 male admissions to the Chicago Washingtonian Home dropped from 1,114 to 171 (Stoddard 1922).

Residential treatment for addiction all but disappeared. Facilities were either closed altogether or became prisons, private hospitals, or asylums for the insane. The only remaining treatment centers were very expensive private hospitals or public insane asylums. Professional interest in the treatment of addiction withered and the American Medical Association for the Study of Alcohol and Other Narcotics dissolved in the 1920s (Cherrington 1925).

White identifies eight external and internal causative factors to explain the rapid decline in residential inebriate treatment: economic forces, social and political forces, poorly developed clinical technology, patient selectivity, modality/environmental bias, conflict within the field and with allied fields, ethical abuse, and the problem of leadership succession (White 1998). A brief expansion of each of these factors follows:

- Economic forces: The failure of government to provide structure or support to residential addiction treatment funding left the movement to the whim of the capricious economic marketplace.
- Social and political forces: The attitudinal trend toward criminalization of addiction disorders marginalized and ultimately almost eliminated residential addiction treatment.
- Poorly developed clinical technology: The scientific foundations of residential addiction treatment never gained the respect of either the scientific community or the public at large.
- Patient selectivity: While publicly funded establishments were often burdened with disruptive court-mandated clients, private institutions became adept at accepting only those wealthiest clients with a high probability of success, often engendering public scorn through this process.
- Modality/environment bias: While residential treatment costs more than outpatient treatment, at the same time it self-selects for those later-stage patients who have burned through their resources and thus restricted their ability to afford the treatment they need.
- Conflict within the field and with allied fields: Conflicts within individual institutions, within the field of addiction treatment, and between the field of addiction and that of mental health treatment created an environment in which sustained growth became impossible.

- Ethical abuses: Perhaps even more striking than the abuses themselves, which were significant, was the treatment professionals' refusal to recognize the concerns and complaints of the patients.
- The problem of leadership succession: The visionary and often charismatic founders of the residential treatment movement seemed particularly inept at recruiting and training the new generation of leaders in the field, and many residential addiction treatment programs simply died with their founders.

Over the course of the residential chemical dependency treatments, however, the inebriate homes and asylums did make substantial contributions. These contributions included support for those suffering from chemical dependence, the first professional medicalization of drug and alcohol excess consumption, biological explanations of drug dependence, and recommendations for physical treatment methods. Discussions of the biology and heredity of inebriety helped move treatment from moral instruction to medical treatment. And doctors who treated drunks began to gain legitimacy as physicians who attended to legitimate patients suffering from a real disease.

68.2.3 Residential Treatment in the Mid-Late Twentieth Century

The year 1935 marked considerable advancements in the treatment of addiction in the United States. First it observed the meeting of an alcoholic New York stockbroker and an alcoholic Akron, Ohio, physician which culminated in the founding of Alcoholics Anonymous (AA). And it commemorated the opening of the first federally supported residential drug treatment center called the Addiction Research Center (ARC) in Lexington, Kentucky. Researchers at ARC spearheaded the study of addiction as a disease in a residential setting, and their work continues today at the National Institute of Drug Abuse in Baltimore, Maryland (White 1998). 1935 was also noteworthy for the founding of residential addiction treatment based on Pavlovian aversive therapy. Seattle businessman Charles Shadel's quest for a solution for his own alcoholism had brought him to Dr. Walter Voegtlin, a gastroenterologist who had just created a treatment for alcoholism based on the use of nausea as a conditioned reflex. Shadel was so impressed with the successful results that he first provided treatment services in his own home and then bought another house to institutionally treat patients and soon thereafter a second institution in Portland. In short, patients were carefully screened for motivation to stop drinking altogether. They were admitted and provided with as much alcohol as they wanted to drink, coupled with injections of emetine to induce vomiting. These treatments were repeated every other day for 10 days and then repeated regularly following discharge for the next year. As with other aversion therapy treatment centers, patients were provided with other detoxification medications, counseling, improved nutrition, sympathetic staff, and a generally supportive environment. The Shadel hospitals were later purchased by Schick Laboratories and operated under the name of Schick-Shadel in Texas and California. A subset of the original Shadel system was later operated under the name Raleigh Hills and franchised into ten states and 21 separate hospitals.

The period between 1948 and 1950 saw the development of the "Minnesota Model" developing from the influence of three separate institutions: Pioneer Hospital, Hazelden, and Willmar State Hospital. This model went on to influence alcoholism and addiction treatment for the next 65 years, and there seems to be no indication that this influence will diminish into the foreseeable future.

In the late 1940s, the welfare department of the city of Minneapolis, Minnesota, became increasingly aware of the rising successes of those residents who became engaged in the fledgling Alcoholics Anonymous. Funding was identified and a new treatment facility was created under the direction of a local sober member of AA. Named Pioneer House, the new treatment program was described as neo-Washingtonian. Patients were given a copy of Alcoholics Anonymous (The Big Book) and Twelve Steps and Twelve Traditions upon admission and the treatment philosophy was based on flexibility and spirituality.

As Pioneer House was just getting underway, Hazelden began to come together as a "sanitorium for curable alcoholics of the professional class" (White). Again, the treatment philosophy was to be founded in AA and the early staff was led by a sober AA alcoholic. Detoxification was generally "cold turkey" but medications were prescribed at times for severe situations. Treatment consisted of lectures, mutual support, improved nutrition, and occasional recreational activities. The facility had four requirements of their patients:

1. "Practice responsible behavior."
2. "Attend the lectures on the Steps."
3. "Associate and talk with the other patients."
4. "Make their beds."

With the exception of only minor creative flexibility in those earliest days, the treatment was simply pure AA.

The 28-day inpatient, abstinence-based, program of treatment was initially developed over a period of 3 years, from 1952 to 1955, by junior clinicians at Willmar State Hospital in Minnesota. Their work would evolve to become known as the Minnesota Model of addiction treatment, which arose from the co-integration of a state hospital program and a nonprofit AA recovery program. The Minnesota Model gained widespread acceptance in the 1970s and became the standard for rehabilitation treatment through the 1970s and 1980s.

As described by William White, there were several components that contributed to the "Minnesota Model" formula (White):

- Alcoholism is an involuntary, primary disease that is describable and diagnosable.
- Alcoholism is a chronic and progressive disease; Barring intervention, the signs and symptoms of alcoholism self-accelerate.
- Alcoholism is not curable, but the disease may be arrested.
- The nature of the alcoholic's initial motivation for treatment – its presence or absence – is not a predictor of treatment.
- The treatment of alcoholism includes physical, psychological, social, and spiritual dimensions.
- The successful treatment of alcoholism requires an environment in which the alcoholic is treated with dignity and respect.

- Alcoholics and addicts are vulnerable to the abuse of a wide spectrum of mood-altering drugs. This whole cluster of mood-altering drugs can be addressed through treatment that defines the problem as one of chemical dependency.
- Chemical dependency is best treated by close, less-formal relationships with their clients and whose activities are integrated within an individualized treatment plan developed for each client.

The founders of the Minnesota Model describe their program stemming from two key principles: (A) respect for individual patients/clients and their families and (B) recovery is possible with the help of a Higher Power and the fellowship of AA (Anderson et al. 1999). Further key elements of the Minnesota Model include the following seven elements: "(1) the integration of professional staff with trained recovering alcoholics; (2) the focus on the disease concept and our link to the 12-step fellowships; (3) the dedication to family involvement; (4) the insistence on abstinence from the use of all addicting drugs (for example, people addicted to alcohol were not considered clean and sober if they used marijuana or cocaine and vice versa); (5) the emphasis on patient and family education; (6) an individualized treatment plan; and (7) a continuum of care integrating sustained aftercare into all treatment plans" (Anderson et al. 1999).

Twenty-eight-day programs typically begin after a patient has undergone medically managed withdrawal from any alcohol, sedative, or opioids they may have been taking. The most effective treatment for alcoholism includes an orientation to AA, an expectation of "step work," groups that combine confrontation and support, lectures, one-to-one counseling, and the creation of a dynamic "learning environment." Based on a 12-step model of spiritual awakening, patients are educated about the disease model of addiction, relapse prevention, and the 12 steps of Alcoholics Anonymous (or Narcotics Anonymous) through didactic sessions. Small group therapy sessions are typically the core of treatment, where patients are encouraged to share their stories and present assignments related to their recovery. In its current iteration, these treatment modalities are often augmented with individual therapy sessions, specialty groups, fitness programs, mindfulness exercises, acupuncture, and a myriad of other approaches.

The most viable, ongoing, sobriety-based support structure for clients following treatment is AA.

In recent years the Minnesota Model has at times endured criticism for being too rigid, but in the early years, the treatment model was quite flexible. Outcome studies seemed good for the time and others soon began to follow this model. According to William White, the reasons for the spread of the Minnesota Model are as follows (White):

- The AA network
- Professional conferences, particularly the Yale-Rutgers Summer Schools
- The educational campaign of the National Council on Alcoholism
- Former clients
- Internship and training programs
- Visitors to Willmar and Hazelden
- Former staff of Willmar and Hazelden

By 1960 the Unites States was home to approximately 200 alcoholism treatment centers, some of longstanding presence and others founded within the preceding 2 decades. Some of the long established programs included the Washingtonian Homes, the Keeley Institute, the Keswick Colony, the Menninger Foundation, the Shadel Sanitarium, and the Blythewood Sanitarium. Some of the newer residential treatment facilities included Mrs. Pink's Place, the Bridge House, Beech Hill Farms, Alina Lodge, Portal House, Brighton Hospital for Alcoholism, the Georgian Clinic and Rehabilitation Center for Alcoholism, the Salvation Army, and the Chit Chat Foundation.

In the 1970s, Minnesota Model proponents were successful in some jurisdictions at requiring insurance payers to include 28-day inpatient stays for substance use disorders as a requirement to sell insurance. The late 1980s and early 1990s saw the emergence of managed care, which sought to aggressively control costs through limiting benefits for behavioral health treatments and particularly substance use disorder treatment.

In 1986, President Reagan signed an executive order mandating the federal Drug-Free Workplace program and the Anti-Drug Abuse Act passed, authorizing $4 billion to support law enforcement approaches to fight drugs. The very next year, 1987, saw the United States launch its War on Drugs, signaling a shift away from treatment and toward law enforcement and incarceration approaches to manage drug and alcohol problems.

These led to changes in payer approaches that effectively eliminated 28-day inpatient treatment programs as first-line insurance-financed treatment for substance use disorders (White 1998). The burden of paying for these programs shifted to state Medicaid programs, and by the mid-1990s, many 28-day free-standing centers had closed. Hospital-based treatment units, once focused entirely on the treatment of substance use disorders, consolidated with other forms of psychiatric treatment under the umbrella of mental health or behavioral health. Additionally, programs began to focus services on partial hospital or intensive outpatient levels of care (White 1998).

Despite these changes, 28-day residential inpatient programs remain colloquially synonymous with the term "rehab." Many well-known addiction treatment centers continue to maintain treatment programs organized in the 28-day residential model of treatment, typically on an out-of-pocket fee basis. In contrast, for indigent patients, there remain residential or inpatient 28-day programs for those program meeting criteria for this level of care. These programs are typically funded by state Medicaid programs in combination with local fundraising.

68.2.4 Halfway House Movement

Halfway houses were in no way restricted to addiction and alcoholism treatment but did find significant application in that regard. Throughout history various cultures have utilized the halfway house concept. For well over a hundred years almshouses

and "country farms" had been established places where alcoholics could be sent to sober up. "Temperance hotels" and "lodging rooms" were used similarly. Beginning in the 1930s, however, it appears that after sober Alcoholics Anonymous members began to take in newcomers to establish their own sober foundation, the halfway house concept really began to take hold. Some appeared to focus on alcoholics who might be on their way into a more structured treatment facility. Others seemed to be organized in a way to help alcoholics who were on their way from a structured treatment environment on their way back to society.

While halfway houses differed widely, there were some general commonalities: structured living, peer support, and lifestyle reconstruction (White). Earl Rubington noted "four structured principles" (White):

- Small size
- Simple rules
- Reduction of status differences between residents and staff
- Informality

In 1974 the International Halfway House Association boasted 1,300 members.

In 1975 the Oxford House model arose as an interesting subset of the halfway house concept. Newly sober congressional attorney Paul Malloy was about to be evicted from the halfway house in which he lived. Rather than go back to the street, he and the other residents got together and created the first resident-administered Oxford model halfway house. They took the concept of recovering staff perhaps one step further. Oxford House has no staff whatsoever, only recovering alcoholics and addicts. Average length of stay is 15 months but residents can actually stay indefinitely. All the residents are expected to hold down a job as well as do their share of the chores. Officers are democratically elected in each house. Every new resident is interviewed and must be voted in by the current residents. Relapses are dealt with by a vote of the residents of each house, usually with immediate eviction. Sobriety is of paramount importance, and if a resident is not willing to maintain their own sobriety, they must find another place to live. Within 15 years there were over 200 homes and by 2013 Oxford House could boast 1,600+ homes around the country, each one run by the residents who supported their own house with their own contributions.

The middle of the twentieth century saw other experiments in residential treatment. Teen Challenge was founded in 1961 by the clergy of the Assembly of God Church and operated 40 residential programs around the country.

68.2.5 Therapeutic Communities

The concept of the therapeutic community (TC) first appeared in the Dead Sea Scrolls at Qumron with discussions of the rules of community. Adherents to this concept were expected to follow the ways of the community and live righteously and healthfully. Similar ideas were applied in the inebriate asylums of the nineteenth century and further developed by Dr. Maxwell Jones in the 1950s. The first broad application of the "community as treatment" was developed as

Synanon evolved out of Alcoholics Anonymous by Charles Dederich on the Santa Monica beachfront in the late 1950s. It began as a 2-year residential treatment program but shifted focus toward a place of self-discovery through an alternative lifestyle, moving it away from drug and alcohol treatment into a quest for utopia through the Church of Synanon (Batiste and Yablonsky 1979).

Daytop Village was founded in New York City in 1962 by an order of the Kings County Supreme Court of New York. Despite the cost of long-term housing and board, costs were kept down by the almost exclusive use of former addicts as both the clinical and administrative staff. Under the astute leadership of Msgr. William O'Brien, Daytop grew into a multi-facility, multistate long-term residential treatment program primarily focused on addiction treatment and following the therapeutic community model. Daytop, Phoenix House, and other similar programs proved highly successful with the very difficult population of addicted criminal offenders.

The most comprehensive evaluation of the therapeutic community model has been done by George DeLeon in his book *The Therapeutic Community*. Despite the positive outcome studies, several documenting success rates well above 90 %, many are still critical of this proven modality.

Most of the therapeutic communities of the late twentieth and early twenty-first centuries relied heavily on government support for their existence (Delancey Street in San Francisco being a stark exception). While they enjoyed high rates of long-term success (no drug and alcohol use and no criminality) at very low relative cost, the governmental funders first in Europe and then in the United States saw them as the geese laying golden eggs. Over time, more and more nonclinical demands were placed on the therapeutic communities while their funding was whittled away year after year. Demands were made to include educational components, health care, and psychiatric management. Government agencies which were unable to deal effectively with the severely mentally ill and otherwise mentally handicapped began to require that the therapeutic communities accept all that were referred their way. The programs were required to hire state licensed personnel, often without the clinical skills of the traditional ex-addict staff who were the key to the dramatic success of the early therapeutic communities. Often these clinical demands were not balanced with commensurate funding, further aggravating the situation. In fact, government agencies frequently pressured therapeutic communities to continually decrease their length of stay, abbreviating the residents' clinical exposure to the point that the programs began to become ineffective.

One shift in the approach of punishing addicts came with the passing of California Proposition 36 into state law, which is also referred to as the Substance Abuse and Crime Prevention Act of 2000, wherein qualified convicts of nonviolent drug possession charges were placed on probation and referred to identified drug treatment programs in the community instead of fulfilling a traditional sentence in jail or on probation without treatment. Treatment programs included residential treatments and aftercare services for approximately 12–18 months (Longshore et al. 2005). The law went into effect on July 1, 2001. Within the first 4 years, there was a 71 % drop in drug use in the nearly 48,000 people that completed treatment (Anderson et al. 1999).

The Greenhouse Program at Bellevue Hospital was a novel approach to the treatment of dually diagnosed persons in a modified TC. It was a peer-led program, with hired staff, based on the structure of TCs for "singly diagnosed substance-dependent patients." It was located in one section of the Bellevue Homeless Shelter in New York City. The first 100 patients had a 33 % completion rate (which is similar to that of Prop 36) and all were abstinent for the duration of their time in the program. Despite this success and over a decade of building a community that patients returned to even after completion of the program, funding was eventually cut leading to the dissolution of the program (Westreich et al. 1996).

Another bright spot is a residential treatment program founded in San Francisco by Mimi Silbert in 1971. Delancey Street describes itself as a "residential self-help organization for former substance abusers, ex-convicts, homeless and others who have hit bottom" and avoids the term therapeutic community (Delancy Street Foundation. http://www.delancystreetfoundation.org/wwa.php). But there are some similarities with the traditional TC of the 1960s. A strong emphasis is placed on the "total learning center" approach, encouraging "financial self-sufficiency and teaching residents self-reliance and life skills." There is no clinical staff; the entire program is resident-run. Average length of stay is 3–4 years and the minimum residential commitment is 2 years. Delancey Street currently boasts five residential facilities with 1,200 total residential beds. While Delancey Street does accept donations of goods (beds, building supplies, etc.), they do not accept any government funding whatsoever, and never have. They do run a variety of enterprises including restaurant, café, digital print shop, moving and trucking business, and several other businesses. In this day of diminishing public funding, this model may be the best alternative for many who suffer from the disease of addiction.

68.3 Conclusion

Despite a history beginning several centuries ago, the future of residential care in the treatment of substance use disorders remains uncertain. During the 1970s, there was an expansion of residential treatment centers particularly with the advent of the Minnesota Model. However, this eventually contracted due to a lack of support and recognition. The overall decline of such programs has left a huge treatment void in Europe, and the United States seems not to be learning from their experience. It is worrisome to consider the defunding of public treatment programs, drying up of insurance funding as health care becomes nationalized, and the fact that private programs are becoming exorbitantly expensive for the common man. Sadly, we may be seeing the next pendulum swing away from addiction treatment and back toward incarceration and this at a time when the world's economies are least able to squander resources on such wasteful and unsuccessful practices. The future of addiction treatment worldwide may well be correlated with appreciating that access to residential treatment is the key in the continuity of care of persons with addiction.

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Strategies of Drug Prevention in the Workplace: An International Perspective of Drug Testing and Employee Assistance Programs (EAPs)

69

David E. Smith and Leigh Dickerson Davidson

Contents

Abstract

Drug testing in the workplace is not universal and is regulated by various governmental agencies at the federal, state, and municipal levels, as well as by various industries. Safety-sensitive occupations are typically targeted, and various industries and agencies have differing drug testing protocols. In the United States, drug testing is highly structured, and much of it falls under the purview of a Presidential Executive Order issued in 1986 and subsequent legislation, establishing a drug-free workplace. A medical review officer (MRO) resolves questionable false-negative and false-positive tests. In European Union countries, drug testing is much less uniform, as attitudes to workplace drug problems are quite variable with no standard approach. While illicit drug use spurred widespread drug testing in the United States, legitimately prescribed medications that may impact safety in the workplace are a growing issue that has not yet been fully addressed. Many companies establish employee assistance programs (EAPs), which are designed to help businesses address productivity issues by providing various services to behaviorally affected employees to alleviate and

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resolve issues, including substance abuse, with their job performance. It is easier to evaluate the effectiveness of the US method, due to its structure, than to assess the varied European approach.

Abbreviations	
AA	Alcoholics Anonymous
ASAM	American Society of Addiction Medicine
CSAT	Center for Substance Abuse Treatment, SAMHSA (U.S.)
DAWN	Drug Abuse Warning Network (U.S.)
DOT	Department of Transportation (U.S.)
EAPA	Employee Assistance Professionals Association
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
EAP	Employee assistance program
MRO	Medical review officer
NCADD	National Council on Alcoholism and Drug Dependence (U.S.)
NIDA	National Institute on Drug Abuse (U.S.)
NSDUH	National Survey on Drug Use and Health (U.S.)
OTC	Over the counter, i.e., medications available without a prescription
SAMHSA	Substance Abuse and Mental Health Services Administration (U.S.)
SAP	Substance Abuse Professional

69.1 Introduction

Drug testing to promote workplace safety by preventing (or at least reducing) employee drug use is regulated by various governmental agencies and at the federal, state, and municipal levels. Employers' insurance companies may require drug testing programs. Different protocols exist for various industries and agencies, although certain elements are constant. Some companies require testing of every employee, others require preemployment testing, and still others require testing for employees holding safety-sensitive positions. Most require testing for drug and alcohol use following accidents. The consequences of verifiable illicit drug use in the workplace range from some form of disciplinary action to referral for treatment to termination of employment.

69.2 Drug Prevention in the Workplace

The modern era of drug use prevention – other than alcohol – in the workplace began in the 1980s in the United States with the establishment of the Drug-Free Federal Workplace Program (Executive Order 12564 1986), which paralleled

the drug epidemic permeating industrial settings in the United States and contributed to a number of highly publicized major, multiple-fatality accidents, in which several of the workers involved tested positive for marijuana. As a result, the US Federal Government issued Executive Order # 12564 in September of 1986:

> The Federal Government, as the largest employer in the nation, can and should show the way towards achieving drug-free workplaces through a program designed to offer drug users a helping hand and, at the same time, demonstrating to drug users and potential drug users that drugs will not be tolerated in the Federal workplace . . ..

The executive order mandated that most of the federal agencies under the purview of the Executive Department require their employees to refrain from the use of illicit drugs, that the agencies implement and develop employee assistance programs, and that they implement drug testing programs and procedures. The focus of the drug-free workplace was to eliminate illicit drug use such as heroin, cocaine, amphetamine, marijuana, and 1-(1-phenylcyclohexyl)piperidine (PCP), known as the "NIDA-5" ("NIDA" being the National Institute on Drug Abuse). However, because alcohol was and is the primary drug problem in industry in both the United States and worldwide, the Omnibus Transportation Employee Testing Act of 1991 included alcohol. As determined by the Division of Workplace Programs of the Substance Abuse and Mental Health Services Administration (SAMHSA) in the United States, the majority of current illicit drug users are employees, as full-time workers constitute about two-thirds of the adult population (unemployed individuals have a higher rate of substance use behaviors and disorders) (Larson et al. 2007).

While illicit drugs were the main impetus for the establishment of the drug-free workplace regulation in the 1980s in the United States, legitimately prescribed medications, primarily opiates, are a growing issue that has not yet been fully addressed.

The components of a comprehensive Drug-Free Workplace Program in the United States include a formal written policy, an employee assistance program, supervisor training, employee education, and methods for detecting illicit drug users (i.e., drug testing). Not all companies in the United States have comprehensive workplace programs.

In addition, US legislation established the designation of "medical review officer" (MRO) for the evaluation of questionable drug test results. Organizations such as the American Society of Addiction Medicine (ASAM) offer regularly scheduled courses to provide clinical training in the review and analysis of drug test results and certification of qualified MROs (ASAM 2005/2009).

Many companies internationally have established employee assistance programs (EAPs), which are designed to help businesses address productivity issues by providing various services to behaviorally affected employees to alleviate and resolve issues interfering with their job performance (Office of Disability Employment Policy 2009). The Employee Assistance Professionals Association lists several national and regional EAP associations and organizations at www.EAPASSN.org.

69.2.1 Drug Testing in the US Workplace

Workplace drug testing in the United States is highly structured and intended to foster workplace safety standards. Tests are generally administered in a nonmedical setting, where body fluids, most commonly urine, are collected and analyzed, passing through a rigorous and well-documented "chain of custody" process (ASAM 2002/2012). The frequency, type, and drugs tested for typically depend on the industry and various governmental regulatory bodies involved. Companies and organizations with US government contracts must be compliant with governmental regulations regarding drug use in the workplace.

Drug testing is most common in settings where employees perform hazardous tasks such as operating heavy equipment and where they could place other persons at risk, as in transporting passengers or performing medical and surgical procedures, in the operation of nuclear power facilities, and in public safety positions such as police and fire. Each branch of the military has a program for drug testing of its service members.

Several types of drug testing exist: applicant, accident/unsafe practice, reasonable suspicion, follow-up to treatment, random, and voluntary. Many employers require drug testing of potential employees; all require drug testing of employees involved in accidents (accident/unsafe practice). Drug testing may also be ordered if an employee's performance is impaired (reasonable suspicion) and/or the employee has been observed using alcohol and/or other proscribed substances.

Follow-up drug testing is often instituted as part of an individual's plan for recovery after intensive treatment. Ideally the tests are random. Voluntary tests might be characterized by an individual desiring to know his own level of substance levels, perhaps in anticipation of an employer test.

Interpreting drug test results is more nuanced than a simple "positive" or "negative" if a valid result is to be obtained. Individuals may test positive if they are taking a prescribed pain reliever, for example. They may test negative if a test is compromised or adulterated either intentionally or inadvertently. For this reason, it is advisable that a qualified medical review officer (MRO) be available to certify the results obtained. It must be noted that while MRO protocols, supplies, and equipment are quite rigorous to prevent adulteration of samples, the Internet and human initiative offer an ever-growing fount of information for bypassing the procedures. Medically prescribed drugs and dental procedures can skew results, and the new synthetic drugs that are continually emerging typically do not even show up in the standard assays (ASAM 2002/2012).

Use of a drug is not associated with impairment and risk of accident. Therefore, in the United States, the focus has been on total drug use prevention, rather than impairment and accident risk.

Random drug testing is mandated by many regulatory agencies to more accurately gauge whether the employees they are regulating are using illicit substances. Employee identifications are usually generated in a random fashion, and the employee must report for a drug test typically within 24 h at a location determined by the employer. A specimen is collected and, depending on the technology

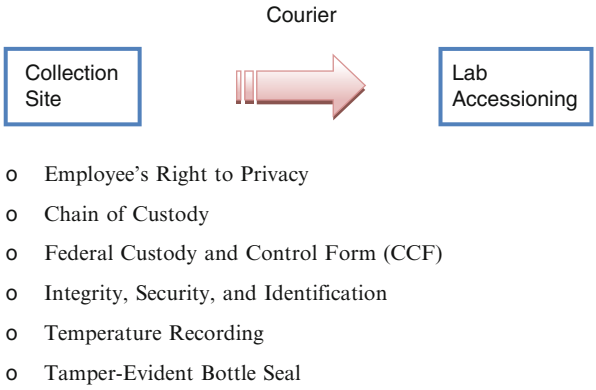

Fig. 69.1 Components of specimen collection

available, is either analyzed digitally on site immediately or shipped via overnight express to a centralized laboratory. Samples are usually "split" in the event of a need to reanalyze, e.g., if a sample is positive and the employee protests the result. At this point the MRO would become involved and order a retest of the split specimen to validate the results of the original test.

The specimen collected, often urine, but possibly other bodily fluids such as blood or hair, follows a rigorously controlled path to control for and balance various concerns such as the employee's right to privacy and the possibility of tampering (Fig. 69.1).

Employees testing positive are often relieved of duty until positive drug test results are resolved by the MRO. The specimen may have been collected incorrectly, subjected to shipping delays, or otherwise mishandled. Employees may also be using over-the-counter (OTC) or prescribed medications that can alter results. Depending on the sensitivity of the tests being used, foodstuffs, e.g., poppy seeds, may also generate a false positive. For this reason, workplace testing in the United States has established cutoff levels for opiates well above the levels triggered by poppy seeds, and for marijuana, well above the levels of passive inhalation ("second-hand smoke"). The test, however, is geared to established drugs. There are many designer drugs such as the synthetic stimulants, e.g., "bath salts," and synthetic cannabinoids, e.g., "spice," designed to create a high for the individual but not registering on the NIDA-5 tests.

Upon resolution of the questionable test results by the MRO, the employer is notified of the validated results. The employer then takes appropriate action as specified by the regulatory agency – ranging from return to work to referral to treatment to termination of employment.

Drug testing is crucial for effective identification, intervention, and monitoring in the workplace. A drug test is a medical test, although it may be used for nullification purposes as well as monitoring the effectiveness of treatment. The medical review officer categorization was established so workers would not be denied medically prescribed medication in overzealous attempts to extinguish illicit drug use. The following illustrates the MRO Drug Test decision tree and laboratory analysis (Figs. 69.2, 69.3, and 69.4).

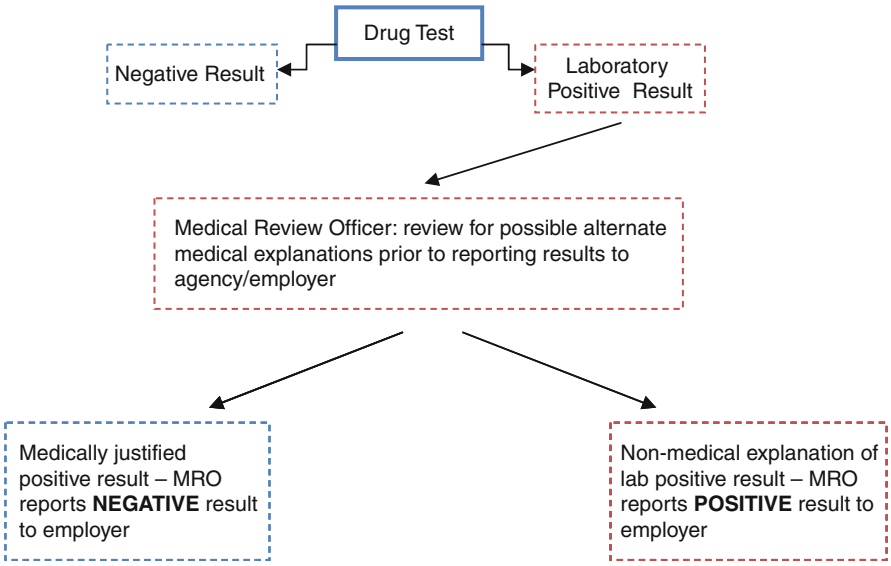

Fig. 69.2 The MRO chain

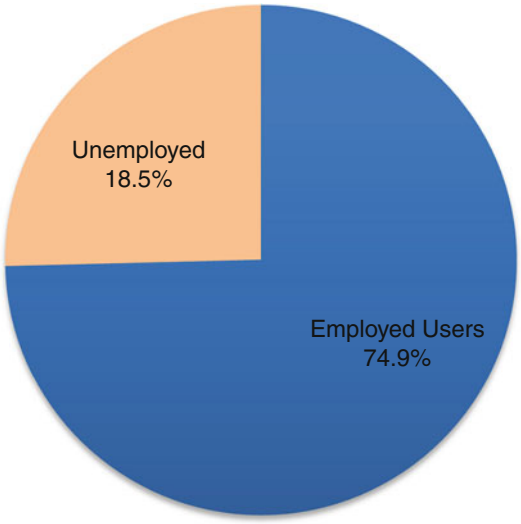

Fig. 69.3 The majority of current drug users are employed (current users of illicit drugs, ages 18 and over) (Source: National Survey on Drug Use and Health: National Findings 2006)

The drugs most often used in the United States are pain relievers. As these drugs are often opioids, they can compromise NIDA-5 results, requiring further validation of the drug test by a medical review officer (MRO).

Companies involved with transportation and use of motor vehicles are usually governed in the United States by the Department of Transportation (DOT) regulations, which specify testing for five illicit drugs: marijuana, cocaine, amphetamine,

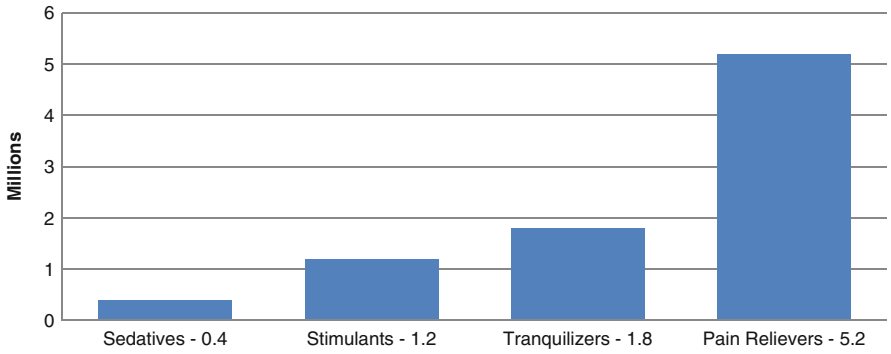

Fig. 69.4 Current use of psychotherapeutic drugs (Source: National Survey on Drug Use and Health: National Findings 2006)

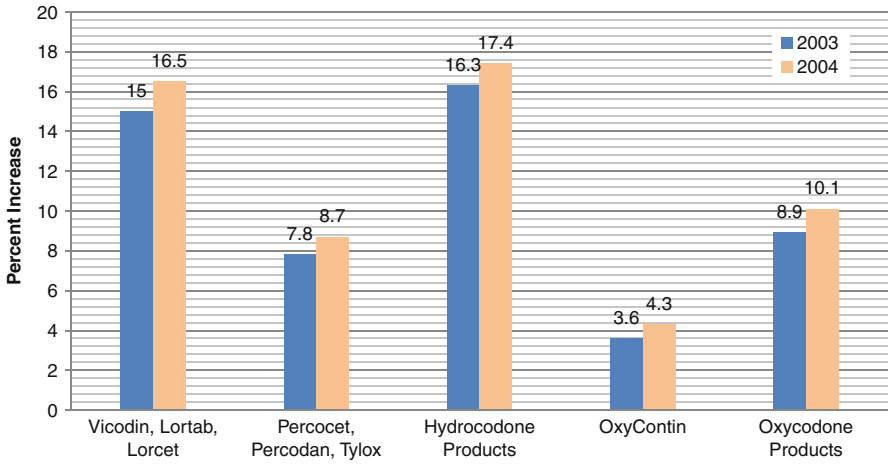

Fig. 69.5 Increase in prescription drug use (Source: National Survey on Drug Use and Health: National Findings 2006)

1-(1-phenylcyclohexyl)piperidine (PCP), and heroin (the NIDA-5). However, there is a growing problem with prescription drug abuse in society as a whole and in the workplace.

The Drug Enforcement Administration (DEA) statistics report that more than six million people in the United States abuse prescription drugs and new drug users use more pain relievers (2.4 million) than marijuana (2.1 million) or cocaine (one million) (Fig. 69.5).

Currently, the prescription drugs most often abused in the United States are opiates, opioids (including codeine, hydrocodone, hydromorphone, oxycodone, oxymorphone, meperidine, tramadol, and fentanyl), benzodiazepines, muscular relaxants, antidepressants, and anticonvulsants.

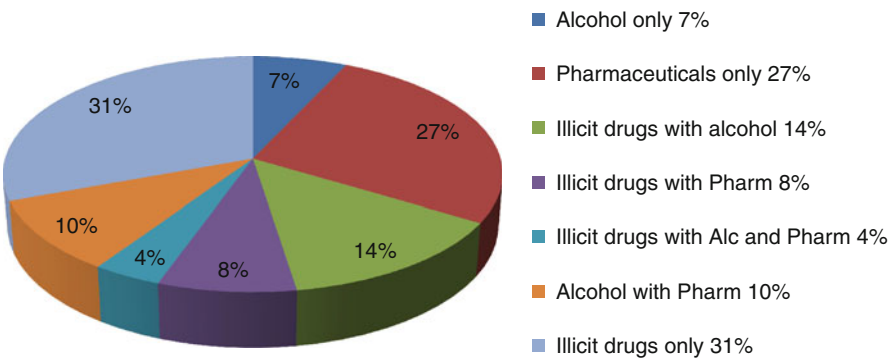

Fig. 69.6 Drug-related ER visits, by type of case: 2005 (Source: SAMHSA, ED Trends from the DAWN Final Estimates 2009)

Since many workers use narcotic pain medication appropriately with physician prescriptions, differentiating between appropriate use, misuse, abuse, addiction, and drug diversion in the workplace is crucial so legitimate pain management is not confused with inappropriate use that produces health consequences and safety risk. When an employee's tests results indicate a positive, the medical review officer (MRO) notifies the employee about his positive test result and requests a copy of the prescription (which should be of recent origin). The MRO instructs the employee to stop work immediately and report to his supervisor. If the employee has no prescription to explain the positive result, the MRO then notifies the employer that the employee is not medically cleared to return to work.

Opioids, unless carefully monitored, even when used for appropriate pain management, can lead to workplace accidents and a variety of related medical, psychological, and behavioral problems. Problems with opioids include side effects such as drowsiness, inattentiveness, impaired judgment, and poor hand/eye coordination; tolerance and physical dependence; loss of function; perception of emotional pain as physical pain (chemical copers); and hyperalgesia.

An issue that has not yet been satisfactorily addressed is establishing protocols for appropriate use of prescription medications that can affect workplace performance. Among the factors involved in the United States is the role of the Americans with Disabilities Act (ADA), which prohibits discrimination against those with disabilities. That is, if an individual requires a medication to maintain a certain quality of life, will denying that person employment due to his medication impair his quality of life?

The medical review officer (MRO) course presented by the American Society of Addiction Medicine (ASAM) provides clinical training on intoxication, overdose, and addiction for the opioid and opioid class of drugs. The course also provides training on the stimulant class of drugs such as amphetamines, methamphetamine, and cocaine, which are widely misused and abused in the workplace (ASAM 2005/2009).

Table 69.1 Levels of alcohol intoxication

BAC (blood alcohol concentration)	% of drivers too intoxicated to drive	Increased risk of accident
0.02 % restraint/awareness	5 %	^1
0.04 % comprehension	15 %	1×
0.06 % judgment	35 %	2×
0.08 % muscle control	65 %	4×
0.10 % coordination	100 %	8×
0.20 % equilibrium/sleep		65×
0.30 % stupor		600×
0.40 % coma		
0.50 % death		

The stimulants are cocaine, amphetamine, methamphetamine, nicotine, and caffeine. The disorders induced, which can affect workplace functioning, include the following, per the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV): dependence; abuse; intoxication; withdrawal; intoxication delirium; induced psychotic disorder, with delusions; induced psychotic disorder, with hallucinations; induced mood disorder; induced sexual dysfunction; and induced sleep disorder.

There are a number of adverse drug reactions that require medical attention whether a drug is legal, such as alcohol, prescribed by a physician, or obtained illicitly through the drug culture, particularly when used in a polydrug combination.

Relative to adverse drug reactions requiring emergency room visits, prescription drugs ranked second and drugs in combination with alcohol ranked third (SAMHSA 2009) (Fig. 69.6).

The relationship between blood alcohol concentration (BAC) and accident risk is well established (the US National Transportation Safety Board (NTSB) is currently campaigning to reduce the legal BAC for all drivers). Due to the rapid metabolization of alcohol, urine ethyl glucuronide (EtG)/ethyl sulfate (EtS) testing allows for the detection of alcohol metabolites in urine for up to about 3 days after alcohol consumption, which standard tests may not detect (Table 69.1).

Identification of a drug problem in the workplace requires appropriate training and professional evaluation. As emphasized by Dr. Westley H. Clark, director of the Center for Substance Abuse Treatment (CSAT) and a faculty member of the ASAM MRO course, a positive toxicology screen or adverse drug reaction does not equate with chemical dependence, substance dependence, or substance abuse. Chemical dependence is often used with such terms as addiction, drug dependence, alcoholism, polydrug abuse, or substance dependence, and it depends on the diagnostic system used in the workplace to determine what the level of drug involvement is for the employee. The most severe form of chemical dependence is addictive disease, which is a pathological state with characteristic signs and symptoms, as well as a predictable outcome if not treated. It is characterized by the compulsive desire for the drug, loss of control when exposed to the drug, and continued use in spite of adverse consequences (ASAM 2005/2009).

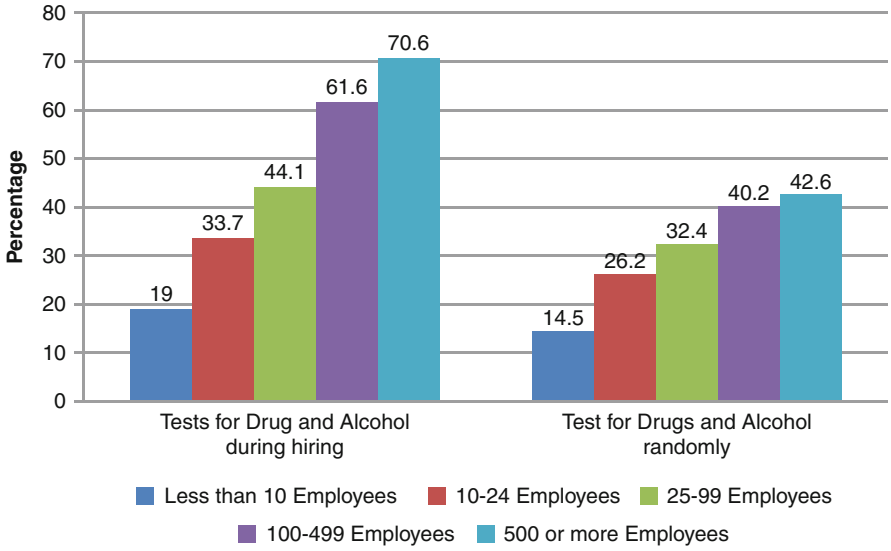

Fig. 69.7 Type of drug and alcohol testing program, aged 18–64 (Source: Worker Substance Use and Workplace Policies and Programs 2007 NSDUH)

Drug testing in the workplace is an essential component of a comprehensive workplace program, but implementation in American industry is quite variable (Fig 69.7).

Indications of treatment for the addicted worker can produce substantial workplace, societal, and personal benefits for both the employee and the company. Studies prepared by the Division of Workplace Programs of SAMHSA have shown that the individual's physical and mental health significantly improve after substance abuse treatment, with a major reduction in healthcare utilization.

Many workers abuse alcohol and illicit drugs in the workplace, violating company policy. However, only about 10 % of this exposed population in the United States display the disease of alcoholism and require longer intensive treatment before returning to work.

Recognizing that addictive drug and alcohol use is a disease has benefits for the employer when the employee is referred to treatment and willing to accept it. If the employee successfully completes treatment, the employer is able to retain a trained, experienced employee and eliminate the costs of recruiting and training a new employee.

69.2.2 Drug Testing in Europe

In European countries, drug testing in the workplace intended to control workplace alcohol and drug use is less standardized and more controversial than in the United States. The conflict revolves around the need for safety in the workplace where

safety concerns are high, such as construction, yet workers' concerns can outweigh the implementation of critical elements of the US testing model. National legislation varies widely in terms of rights and obligations for testing, allowable intake and use of alcohol or other drugs, acceptance of testing, the conditions under which testing can take place, monitoring of tests, and access to the results. Such deviation in policy makes standardized workplace programs associated with testing very difficult across the European Union. Some countries have no specialized programs, and most have limited programs, with the United Kingdom having the most comprehensive program.

Corral et al. (2012) examine in great detail the types of regulation in place across a wide swath of the European countries in their report *Use of alcohol and drugs at the workplace* for the European Foundation for the Improvement of Living and Working Conditions (Eurofound). As in the United States, drug testing is mandated (or not) by a variety of regulating governmental bodies and industries, and in some countries employees have a much louder voice than allowed in the United States. A sampling of study results cited in the Eurofound document follows.

Another major factor is the cultural tolerance, particularly toward alcohol in the workplace, which varies from country to country in contrast to the United States where the model is zero tolerance.

A majority of employers and employees in Europe reject the use of alcohol and drugs in the workplace, but the procedures for implementing this policy are quite varied and strongly influenced by the cultural views of the host country. Furthermore, the cultural stance toward alcohol and drugs in the workplace has grown more conservative based on a variety of studies. The Swedish Construction Federation reported that it was no longer socially acceptable to use drugs in the workplace in contrast to attitudes in the construction industry 30–40 years ago. However, as reported on a presentation of illegal drugs, the topic of drugs in the workplace is still a taboo subject in many member European states.

There is growing awareness of the consequences of alcohol and drugs in the workplace. Ninety percent of Portuguese enterprises had concerns relating to health problems, higher instances of sick leave/short-term absenteeism, reduced performance levels, labor conflicts and an unsettled work environment, and a greater number of work-related accidents. In an Italian study, absenteeism was found to be more than double in Italian employees addicted to drugs than in nonaddicted employees (Mariotti 2004). Alcohol-dependent workers in Austria were on sick leave 16 times more often and were sick 2.5 times more often than those who were not dependent.

Other European studies on drugs and the workplace also demonstrated that alcohol and drug abuse can negatively impact work performance and contribute to workplace accidents. One of the most important negative consequences of alcohol and drug use at work is the increased risk of accidents and potential harm to fellow employees. A 2008 Latvian report indicated that there was substantial economic loss and a damaged public image where the affected employee interacted with the public.

European studies have also documented the large economic costs of substance abuse in the workplace. In Norway, alcohol-related illness represents an economic loss in millions of euros. In Austria, alcohol use accounts for 1.25–2.5 % of the total payroll cost. The Austrian Chamber of Commerce (WKÖ) (p. 35) states that a worker with alcohol and drug problems only performs 75 % of his/her potential output.

Given these significant economic effects, European enterprises are increasing their response to unhealthy alcohol and/or drug involvement in the workplace.

However, it is often some time before a worker's alcohol or drug problem is recognized. A German study indicated that it was 8–10 years for men and 3–5 years for women. The typical response is to dismiss the employee. The workplace strategy of intervention and rehabilitation for first-time offenders widely used in the United States is much less common in Europe.

In contrast with the United States, European countries put more emphasis on workplace conditions that contribute to substance abuse, including work-related and social/personal reasons in which alcohol and illicit drugs are used for coping with their problems.

Work-related reasons include arduous working conditions, irregular work practices, and psychological stress at work.

The European Workplace Drug Testing Society (www.EWDTS.org) is organized to examine issues relating to workplace drug testing and presents annual conferences on the topic, bringing together various stakeholders: employees, employers, human resources, occupational health, compliance officers, attorneys, drug counselors, and treatment providers. EWDTS' stated goal is to ensure that drug testing in Europe is performed in a standard and legal manner. Their website also offers brief summaries of the status of workplace drug testing in various countries.

There is no centralized statistical information source for Europe. However, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA 2013) reports that cocaine is the second leading drug used after cannabis, with amphetamines and ecstasy a growing problem. If workplace programs exist, they are incorporated into an overall national strategy, with a few exceptions.

In France, the National Research and Safety Institute for the prevention of accidents at work has a program to train employers and managers to identify employees of concern and address their problems. In Germany, the German Centre for Addiction Issues commissioned an expert report on the practice of company-based drug prevention, which in 2006 was debuted by policy makers, health insurers, and social partners.

Various European states have found that alcohol and drugs represent a severe problem for a significant percentage of the working population. National estimates indicate that 5–20 % of workers are impaired by alcohol or other drugs, a problem that is particularly relevant in sectors such as construction, transportation, and farming. Alcohol and drug consumption at work often results in negative workplace consequences in terms of higher incidence of sick leave and reduced performance and productivity, as well as a negative economic impact. However, the United States has more comprehensive data on intervention and rehabilitation of the addicted employee, again highlighting major policy differences.

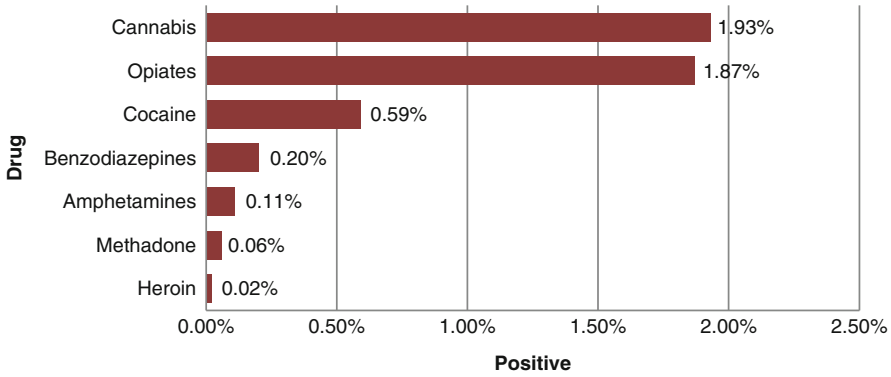

Fig. 69.8 UK drug prevalence within the workplace 2007–2011

Most European countries have some kind of general legislation or agreements in place to prohibit or regulate the consumption of alcohol and other drugs in the workplace, but there is considerable diversity regarding the type of legislation in force and the way policies are implemented. Some countries include the workplace as one area among several for which drug use is addressed. In some countries the approach can be labeled as disciplinary, as the limits on alcohol and drug use in the workplace are established in the national labor code or worker statutes.

In other countries, the approach is more preventative with regulations being established in national health and safety laws. In a small number of countries, such as Germany, Belgium, and Denmark, the regulation of alcohol and drugs in the workplace is based on collective agreements between social partners rather than purely coercive measures.

In some industries, companies institute workplace drug prevention policies because they are operating as multinationals, and drug policies must be in place in certain geographical locales and not others. Airlines and shipping firms illustrate this example.

European studies put more emphasis on work-related reasons for alcohol and drug use, including the existence of demanding physical work, uncomfortable working conditions, and low job satisfaction, including worker rights, whereas in the United States, the emphasis is on zero tolerance. Additionally, European cultures generally have had a more tolerant view of alcohol use during the workday (as was the case in the United States into about the 1980s, giving rise to the concept of the "three-martini lunch"), although some recent reports indicate that this is changing.

In a research report on drug prevalence in the UK workplace by the drug testing provider Concateno (2012), researchers determined that cannabis was the most often used illicit substance, closely followed by opiates (Fig. 69.8).

In comparing the patterns of drugs in the workplace between the United States and the United Kingdom, the positive rate in the United States has decreased,

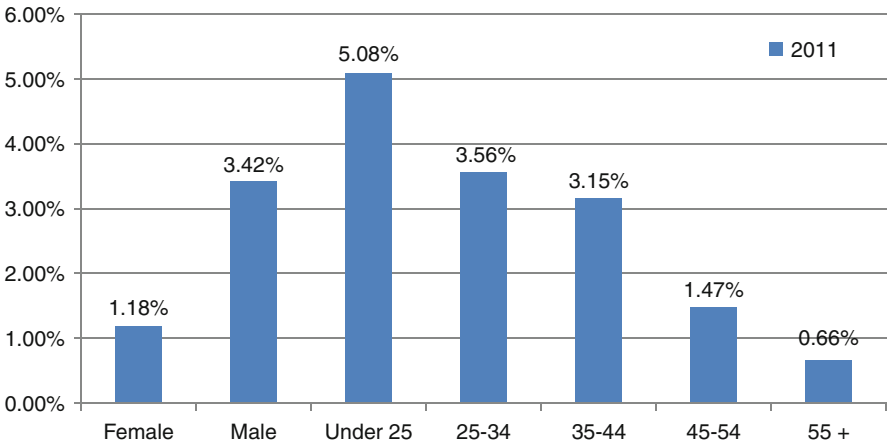

Fig. 69.9 UK workplace drug prevalence demographic for 2011

whereas the UK rate has increased. However, the equivalent rates in the overall populations are approximately the same. The question arises, does variation in workplace strategies between the two countries account for various outcomes? (Fig. 69.9).

The Concateno report further reveals that patterns of drug use change with age. Cannabis use decreases, while use of opiates increases.

A number of European studies have defined patterns of drug abuse in different countries and regions of the world. However, there are far fewer studies of workplace programs, and those that exist focus on the concepts of medical review, addiction medicine, and rehabilitation for the employee. Other countries and continents, particularly in the developing countries, have no studies or uniform policies for alcohol and drugs in the workplace.

As the economy globalizes, much more study is required to determine the most effective workplace programs in order to reduce workplace accidents while providing for the health and safety of the employee as well as increased productivity, which is often the main concern for the employer.

69.2.3 Employee Assistance Programs

Employee assistance programs for alcoholism in the workplace gained prominence after World War II, driven in large part by the influence of Alcoholics Anonymous (AA), which was formed in the 1930s. Individuals influential in the AA movement, such as Marty Mann, who helped found the National Committee for Education on Alcoholism (now the National Council on Alcoholism and Drug Dependence, or NCADD), and Ruth Fox, MD, who helped form the New York Society of Alcoholism, which evolved into the American Society of Addiction Medicine, were

among the guiding forces behind the formation of the American Society of Addiction Medicine (ASAM).

ASAM now recognizes addiction as a disease and has developed a clinical definition for addiction:

> Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors.
>
> Addiction is characterized by inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death. (ASAM 2011)

The 4 C's of Addiction

- Craving
- Loss of Control
- Compulsive use
- Continued use despite harm

The key to an effective workplace program is a good employee assistance program (EAP). Identification of the alcohol- and drug-impaired employee can result in disciplinary termination for the employee and/or evaluation with referral to appropriate treatment. The ASAM assessment and patient placement criteria are most effective for such evaluation and referral. Although companies are not required to have workplace EAPs and treatment programs, many do have them because of insurance and liability issues. SAMHSA has determined that such programs produce excellent benefits, both economic, where treatment saves money in health and social costs, and societal, by reducing health and behavioral problems including accidents.

Because many workers use narcotic pain medication appropriately with physician prescription, differentiation between appropriate use, misuse, abuse, addiction, and drug diversion in the workplace is crucial so legitimate pain management is not confused with inappropriate use that produces health consequences and safety risk. The evaluation and selection of an appropriate lab is essential. It is also crucial to have a qualified medical review officer to interpret the drug test to reduce confusion and inappropriate action on either false-positive or false-negative test results.

EAPs may be funded by employers or by employee benefit organizations such as unions and are usually provided at no cost to the employee. They are designed to provide short-term counseling for a variety of personal issues, including legal, financial, life events, and health, including substance use and misuse, that may affect workplace performance. For issues which cannot be resolved quickly, referrals and other resources are typically provided. One might compare the services provided by an EAP to those of an ambulance: get to the patient quickly, stabilize his condition, and transfer to a longer-term facility for further evaluation and care if necessary.

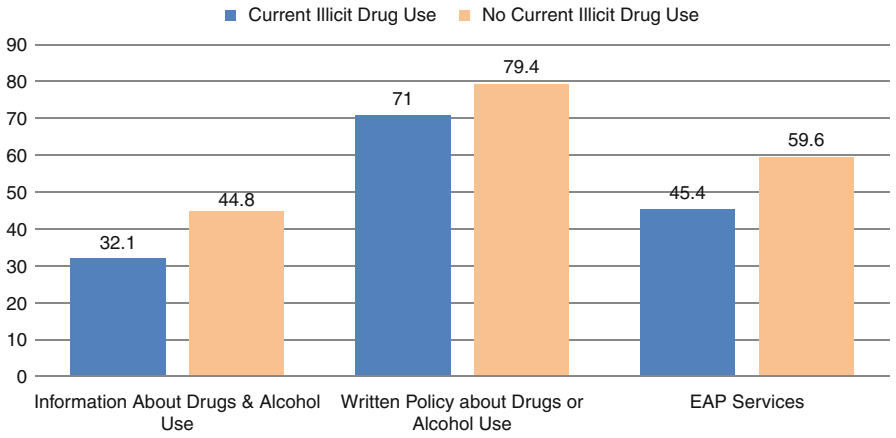

Fig. 69.10 Percentage of full-time workers, aged 18–64, reporting workplace-provided information (Source: 2002–2004 NSDUH, Division of Workplace Programs SAMHSA)

Confidentiality is maintained between employee and counselor; the content of sessions cannot ethically be reported to the employer.

EAPs are available internationally; the Employee Assistance Professionals Association is a worldwide association (www.EAPASSN.org), while several national organizations have their focus on Europe, the United States, Canada, Australia, the United Kingdom, Ireland, or the Asia Pacific region.

EAPs usually have a strong component for the recognition, referral, and treatment of substance misuse and abuse. Some large programs may include substance abuse professionals (SAP), who are trained to identify those with drug issues and provide referrals to treatment. They may also identify practitioners who enable employees who are abusing drugs, misusing their medications, or diverting their prescribed medications for sale to others for profit. Since the provision of prescription drugs is often an employer-paid benefit, identifying prescription misuse can ultimately save the employer funds that can be used in other areas to benefit employees (Fig. 69.10).

The EAP may also play a role in monitoring the return to work of a person with addictive disease, thus providing the employer with the experience and expertise of a trained employee and reducing the costs of recruitment and training of a new employee. Monitoring would typically consist of more frequent random drug testing of the returning employee, in conjunction with regularly scheduled psychotherapy meetings, using a 12-Step or other model.

69.3 Conclusion

In reviewing the broad topic of drugs in the workplace from an international perspective, it is clear there is no uniform approach.

The United States has the most well defined and structured approach, with elements of strict discipline, mandates, treatment, and rehabilitation with drug test monitoring before reentry into the workplace. In the European Union, there is a much broader approach that includes workplace conditions and reasons for alcohol/drug use with a focus on prevention but relying on rehabilitation.

Employee assistance programs offer benefits to both employers and employees. For the employer, they provide an avenue for maintaining productivity, reducing absenteeism and workplace accidents, and retaining skilled employees. For the employee, an EAP provides a lifeline to the recognition of and referral to treatment for debilitating substance abuse.

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Treatment in Criminal Justice Settings

70

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Abstract

The high prevalence of use among offenders is a consistent trend that transcends international boundaries. Chronic drug users in the criminal justice system pose risks to themselves and the general population through their commission of drug-related property and violent crime, as well as through the spread of infectious diseases, such as HIV and HCV. In this chapter, we review multinational evidence concerning the drug/crime relationship, the use of drugs within correctional settings, the consequences of drug use among offenders, and the intervention approaches for drug-involved offenders in custodial settings as well as those under community supervision. We conclude with several recommendations for practice and research that we consider to be important next steps in advancing this literature: (1) focus on implementation; (2) need for more randomized trials; (3) clarification of the role of coercion – when it helps, when it hurts; (4) distinguish "addicted offenders" from "offender addicts"; and (5) examine the use of depot medications for opiate-dependent offenders.

70.1 Introduction

The prevalence of substance use and substance use disorders among criminal justice populations has remained consistently high for decades – and in some places it continues to increase. It is estimated that half of prisoners in the European Union have lifetime histories of heavy drug or alcohol use (Zurhold et al. 2004). In the United States, the prevalence is estimated at nearly 85 % (Center on Addiction and Substance Abuse [CASA] 2010). Even as US incarceration rates are on the decline, the percentage of offenders incarcerated for drug charges has increased by nearly 20 % (CASA 2010).

The high rates of substance use among criminal offenders are the result of a host of demographic, psychological, sociological, and legal factors that vary across cultures. But despite these variations, one overall trend is clear: In most countries, substance-involved offenders account for a substantial share of criminal activity and criminal justice costs. According to one review, drug offenders account for 3–29 % of those incarcerated in the European Union (EU), 4–29 % of inmates in non-EU European countries, 5–53 % of inmates in the Americas, and 10–58 % of inmates in Asia/Oceania (Bewley-Taylor et al. 2009).

In this chapter, we review multinational evidence concerning the drug/crime relationship, the use of drugs within correctional settings, the consequences of drug use among offenders, and intervention approaches for drug-involved offenders in custodial settings as well as those under community supervision.

70.2 The Evidence for Causes, Consequences, Treatment

70.2.1 Causal Effects of Illicit Drugs on Criminal Behavior

Because the association between drug use and crime is complex, Goldstein's (1985) conceptual framework for the various types of drug/crime relationships is widely accepted and deserves some discussion here. Although originally proposed to explain the relationships between drug use, the drug trade, and violence, this framework can be applied more generally to include property offenses as well. Goldstein argues that drug use can be associated with other forms of criminality because of economic-compulsive, pharmacological, and systemic models of use and/or distribution. These are briefly summarized below:

- Economic-compulsive – resorting to criminal behavior to support one's drug use. Crimes in this category include property crimes to obtain money for drugs, selling drugs to support one's own habit, or having sex with someone in exchange for drugs or money for drugs.
- Pharmacological – engaging in irrational or violent behavior as a result of the acute and/or chronic psychological or physiological effects of a drug. For example, certain offenders might use, or threaten to use, violence because they were intoxicated and were not aware of what they were doing; or in some cases, an offender might use drugs or alcohol expressly to reduce the fear of danger prior to engaging in a criminal act.
- Systemic – engaging in crimes ranging from selling drugs to using violence, or the threat of violence, to protect a drug operation.

Subsequent research testing these relationships has shown that the systemic factors offer the strongest link – particularly for violent crimes (Tardiff et al. 1986). Evidence for the pharmacological link to violence among humans is often confounded by the poor specification of what drugs were used and in what quantity. Cartier and colleagues (2006) examined data from over 600 prison parolees to explore the associations between methamphetamine use and recidivism and found that methamphetamine use was significantly predictive of self-reported violent criminal behavior and general recidivism (i.e., a return to custody for any reason). This analysis controlled for background differences in demographic and criminal history, but was limited to the narrow range of variables available. More controlled animal studies have examined aggressive behaviors (number of initiated bite attacks and latency before attacks) between mice that had received a single injection of methamphetamine versus chronic injections over 8 weeks. The authors found that the single injection did not increase fighting, but chronic injections were associated with increased attacks and decreased latencies in attack behaviors (Sokolov et al. 2004).

Another method to assess the relationship between substance use and crime is to directly ask arrestees whether their drug or alcohol use was a factor in their commission of the arresting offense. Using data from the Drug Use Monitoring in Australia (DUMA) database, Payne and Gaffney (2012) found that 45 % attributed their current offense to either alcohol or drug use. The highest attribution rate was found among heroin users (54 %), followed by alcohol users (41 %).

70.2.2 Drug Use Behind Bars

The research base on drug use in prison is limited. Most of the studies on this topic have been conducted in the United States, Great Britain, and Canada. In the United States, estimates of in-prison drug use based on random drug tests have ranged from 1 % to 27 % (Vigdal and Stadler 1989; Inciardi et al. 1993). Using a combination of convenience and random sampling to survey 1,054 prisoners in 30 prisons in Kentucky, Tennessee, and Ohio in 2001, Gillespie (2005) found that 35 % reported some behavior in the past 12 months related to drug and alcohol use (use and possession, but also manufacture and sale).

Studies in the United Kingdom have revealed even higher prevalence of use in prison. According to Shewan et al. (1994), 74 % of inmates surveyed in four Scottish prisons reported using marijuana while in prison. Using a sample of offenders who had used drugs prior to prison, Bullock (2003) found that 56 % of inmates reported using any illicit drug in prison, with marijuana being the most common drug, followed by heroin. This study also queried inmates about their frequency of use while in prison, finding that 14 % of inmates interviewed reported using marijuana daily or near daily; the figure for daily heroin use was 3 %.

In an interview study (Pernanen et al. 2002) of Canadian prisons, 29 % of the sample reported using any illicit drug in the 3 months prior to the interview, with the most popular drug being marijuana. Alcohol use was reported by 16 %. Nearly 90 % of those interviewed said that their behavior in the past 3 months was typical of their behavior over the past year or since their arrival in prison. Random drug testing results have also been used to develop estimates for drug use. Kendall and Pearce (2000) reported that the percentage of any positive test across Canadian prisons ranged from 10 % and 13 % between 1994 and 1998, most commonly for marijuana.

70.2.3 Mortality Rates Among Just-Released Offenders

Although prison and jail can be effective at reducing levels of crime and drug use during the period of incarceration, resumption of these behaviors upon release is the norm. In the United States, nearly 7 in 10 released offenders are rearrested within 3 years (Bureau of Justice Statistics 2002). Data regarding drug use are even more disquieting, indicating that in many cases, offenders are re-addicted within 1 month of release from incarceration and their drug use and/or crime levels following prison can even exceed those reported prior to incarceration (Hough 2002).

The risk of death among parolees is particularly high – nearly 13 times greater than those of similar demographic background – during the first 2 weeks following release from prison, with drug overdose being the leading cause (Binswanger et al. 2007). As dire as this finding is, it may be an underestimate of the problem. A study of newly released prisoners in England and Wales found that the mortality rate among males was 29 times higher than that of the general population during the first 2 weeks of release. The mortality rate for female offenders was *69 times higher* (Farrell and Marsden 2007). These studies are included in a recent meta-analysis of

drug-related deaths following prison release that revealed a three- to eightfold increase in the risk of drug-related deaths during the first 2 weeks following release (relative to the subsequent 10 weeks), with relatively high risk of death remaining throughout the first month of reentry (Merrall et al. 2010).

70.2.4 Intervention Settings for Drug-Involved Offenders

In most countries, the criminal justice system encompasses offenders who are incarcerated in jail or prison and those under supervision in the community. The latter group – those on probation or parole – constitutes the vast majority of the criminal justice population. Although the treatments described below can be implemented in custody or in the community, both settings have advantages and disadvantages that merit consideration.

70.2.4.1 Prison and Jail Settings

Because prisons and jails are confined settings, they offer an important advantage over community settings: access to a captive population of high-risk substance misusers. This, combined with the tedium of daily life behind bars, provides ample opportunity to screen, assess, and treat those in need of services. Still, in many countries, limited resources are devoted to security and basic services, with little left for substance abuse treatment services (Dolan et al. 2007). Even in more affluent nations, treatment need often exceeds capacity. In the United States, for example, it is estimated that only about one in four inmates in need of substance misuse treatment receives it (Taxman et al. 2007). There are, however, some challenges associated with custody-based treatment that reduce its appeal. Common elements of traditional drug abuse counseling approaches, such as the assurance of confidentiality and mutual self-disclosure between counselor and client, are limited in prison. Consequently, even experienced community-based counselors must learn to adjust their counseling styles in order to be effective in this environment. There is also a conflict between security concerns and rehabilitative goals, often limiting inmates' movement within a prison that may be required for attending groups, counseling sessions, etc. Lastly, a major limitation to providing pharmacotherapy in jail or prison is the risk that inmates will divert psychoactive medications such as buprenorphine and methadone to other inmates for recreational use (Dolan et al. 2007).

70.2.4.2 Community Settings

An important advantage of community settings is that drug-involved offenders are forced to learn and rehearse abstinence-supporting behaviors in the "real world," where drugs and drug-using peers are readily available. However, once an offender leaves the controlled environment of jail or prison, adherence to medication (Stephenson et al. 2005) and psychosocial treatment (Farabee et al. 1999) declines dramatically. For instance, one study of over 2,000 HIV+ inmates released from prison found that only 18 % filled their ART prescription within the first 30 days following discharge (Baillargeon et al. 2009). Particularly in the contexts of

community-based treatment, coercion through legal pressure is often cited as a useful tool. (Our use of the terms "coerced or compulsory" refers to the use of legal pressure and supervision to ensure that drug-involved offenders enter and remain in substance abuse treatment appropriate to their needs. We do not condone the use of compulsory drug detention centers where those arrested for – or accused of – using illicit drugs are remanded without due process to engage in forced labor and live in substandard conditions.) Indeed, some studies have shown that coerced clients do as well or better in treatment as those entering voluntarily (see Leukefeld and Tims 1998). However, it should be noted that few of these studies have measured coercion directly and that the outcome of interest in most of these studies has been program retention and/or completion rates, rather than reductions in drug use or recidivism (Wild et al. 2002). As a result, the effects of coerced treatment remain unclear.

70.2.5 Intervention Models for Drug-Involved Offenders

The associations between substance misuse and crime, and the public health and safety risks posed by ongoing drug use behind bars, underscore the need for prevention and intervention. What is less clear is how to prevent drug use and provide interventions. In this section, we summarize common approaches to reducing drug use (and its attendant problems, such as recidivism and the spread of infectious diseases) among convicted drug-misusing offenders.

70.2.5.1 Psychosocial Treatments

Psychosocial treatments refer to therapeutic interventions aimed at changing offenders' drug-taking behavior by focusing on root causes (psychological and environmental), proximate causes (learned responses to internal and external cues), drug-related knowledge and attitudes, and behavioral change through rehearsal and role play. Psychosocial treatment is common in correctional settings as it is relatively inexpensive and can occur in groups. Two of the most prominent forms of psychosocial treatment in correctional settings are therapeutic communities (TC) and cognitive behavioral therapy (CBT). A third related approach is the 12-step approach (Alcoholics Anonymous [AA] and Narcotics Anonymous [NA]), though this is technically considered peer-led support rather than treatment. Nonetheless, given the ubiquity of AA/NA groups in correctional settings, we include a discussion of the 12-step approach in this section as well.

70.2.5.2 Therapeutic Communities

Among prison-based substance abuse treatment programs, the most commonly evaluated is the therapeutic community (TC). The TC philosophy holds that substance abuse is not the main cause of the offender's problems. Rather, it is a symptom of a larger problem: the disorder of the whole person. Thus, the goal of a TC is to "habilitate" clients in a holistic fashion, emphasizing personal responsibility. Rather than attempting to change offenders through counselor-led, didactic presentations, TCs rely primarily on the residents themselves to effect change on the individual.

After reviewing 11 evaluations of prison-based TCs, Phipps et al. (1999) reported that two of the TC programs showed clear evidence of an effect, three showed some evidence of an effect, three showed no effect, and three were inconclusive. The reviewers further recommended caution in interpreting this literature because the individual studies varied considerably in terms of their quality and conclusions.

A review by Pearson and Lipton (1999) showed more favorable results for TCs, but no support for other types of prison-based substance abuse programs. Again, however, the reviewers noted the generally poor quality of studies in this area. As mentioned earlier, of the seven therapeutic community evaluations in their meta-analysis, only one was rated "good," with the remainder rated "fair" or "poor." Subsequent reviews of the prison-TC literature continue to report positive effects on drug use and recidivism, but these effects are buttressed by the selection effects of the subgroups of TC graduates who voluntarily enter and complete aftercare programs in the community (Bahr et al. 2012).

The popularity of the prison-based TC approach appears to have peaked in the 1990s and declined over the past decade. This may be attributable to its relatively weak empirical support and the perceived advantages of cognitive behavioral therapy.

70.2.5.3 Cognitive Behavioral Therapy

Cognitive behavioral therapy (CBT) refers to a category of approaches designed to change the way offenders process information and perceive their environment and themselves. These treatments focus on providing offenders with the cognitive skills and behavioral methods needed to identify high-risk situations, dysfunctional attitudes, and effective coping strategies. A recent meta-analysis of 53 controlled trials of CBT for alcohol and illicit drug users found a small but statistically significant effect for this approach, though the effects were largely diminished within a year (Magill and Ray 2009). A separate meta-analysis of 58 evaluations (conducted in the United States, Canada, the United Kingdom, and New Zealand) of CBT for offenders also showed positive effects for this approach on recidivism – with an average reduction of about 25 % in recidivism risk. The authors also drew two important conclusions about moderator effects: (1) the strongest treatment effects were found for the highest-risk offenders, and (2) the "brand name" CBT programs produced effects that were similar to the generic versions (Landenberger and Lipsey 2005).

70.2.5.4 12-Step Programs

Support groups, such as Alcoholics Anonymous and Narcotics Anonymous, exist in countries around the world, especially in the United States, Canada, and Latin America. The general approach of 12-step facilitation focuses on self-help and peer support, with a strict emphasis on abstinence. The anonymous nature of these groups has hampered efforts to subject them to rigorous evaluation, but one Cochrane Collaboration review including eight trials (comprising over 3,000 participants) found some evidence that AA participation may aid in retaining patients in formal treatment, but did not find strong evidence for its direct role in reducing alcohol use (Ferri et al. 2006). Our review did not identify any outcome data specific to correctional populations, but the 12-step approach is extremely popular

in these settings. In the United States, for example, more than a quarter of state prison inmates and about one in five federal inmates meeting criteria for substance misuse participate in such groups (Mumola and Karberg 2006).

70.2.6 Medication-Assisted Treatments (MAT)

70.2.6.1 Enhancing Receptivity of MAT in Correctional Settings

A recent survey of criminal justice agencies affiliated with NIDA's Criminal Justice Drug Abuse Treatment Studies (CJ-DATS) collaborative found that MAT is underutilized in the treatment of US offenders with substance use disorders (Friedmann et al. 2012). Offenders most likely to receive MAT were pregnant women and those experiencing opioid withdrawal. Offenders *least* likely to receive MAT were those reentering the community after serving a prison or jail term. Among the primary factors inhibiting the use of MAT in correctional settings were preferences for drug-free treatment and limited knowledge of the benefits of MAT. Addressing these philosophical- and knowledge-related barriers will require relevant data collected in real-world settings, that is, the testing of practical MAT administration models in offender populations.

70.2.6.2 Methadone

Methadone is a synthetic opioid used to reduce craving and block the euphoric effects of heroin, morphine, and other non-prescribed opioids. It is also used for opiate detoxification. Since the 1990s, following the development of maintenance programs in the community, programs have also been introduced in prisons. In-prison methadone provision is now available in Canada, Australia, Poland, Indonesia, Iran, New Zealand, Puerto Rico, and the majority of Western Europe (Betteridge and Jurgens 2008). After researchers in Tehran found that a history of shared injection equipment in prison was the main predictor of HIV infection in the general population, the Iranian government launched a pilot program to provide methadone to 50 opiate-dependent prisoners. The results were promising enough that over 6 years the program was expanded to 142 institutions – offering MMT to more than 25,000 inmates in 2009 (Farnia et al. 2010). At the present time almost every large- and middle-sized prison in Iran provides methadone treatment to injection heroin users, and as of 2011, there were over 38,000 prisoners in Iranian prisons in treatment with methadone (Momtazi et al. 2012). Iran has developed one of the largest systems of methadone treatment in prisons, supported by a clinical trial in an Iranian prison that demonstrated methadone treatment is associated with a significant reduction in injection drug use (Bayanzadeh et al. 2007; cited in Momtazi and Noroozi (this volume)). During that same year, more than 19,000 MMT treatments were provided to inmates in the United Kingdom (Stover and Michels 2010). A key finding regarding methadone induction for this population is that initiation of MMT prior to release produces significantly better outcomes than offering MMT upon release to the community (Gordon et al. 2008).

70.2.6.3 Buprenorphine

A substantial body of research supports the safety and efficacy of buprenorphine and the buprenorphine-naloxone combination (e.g., Ling and Wesson 2003). A recent review of 24 randomized trials revealed that buprenorphine (at medium to high doses) was significantly superior to placebo medication in reducing heroin use (Mattick et al. 2008). Several properties of buprenorphine may make it potentially less objectionable than methadone to criminal justice personnel as a treatment for opiate dependence. First, the agonist activity of buprenorphine has a ceiling effect that decreases the danger of overdose and limits its abuse liability. Second, buprenorphine produces sufficient tolerance to block the effects of heroin and other opiates, thus reducing illicit opiate use. Third, buprenorphine exhibits a slow dissociation from μ-opiate receptors, which results in a long duration of action and a reduced dosing schedule compared with methadone. Fourth, the combination tablet of buprenorphine and naloxone (as Suboxone) reduces the risk of illicit injection – along with injection-related HIV/HCV risk (a common problem in correctional settings where injection equipment is scarce and sharing is common).

In spite of the substantial literature that has accumulated over the past decade supporting the use of buprenorphine, it has not been readily adopted in correctional settings. A recent survey of the US state and federal prison systems showed that only 15 states (29 %) provide any referrals to community buprenorphine providers (Nunn et al. 2009). Although the use of MAT is more common in jails than in prisons (used primarily to manage opiate withdrawal), it is important to note that it remains unavailable in two thirds of US jails (Oser et al. 2009).

70.2.6.4 Naltrexone

Naltrexone is an opioid receptor antagonist that blocks the euphoric effects of heroin and other opioids. This characteristic has fostered growing acceptance of naltrexone by correctional authorities who wish to avoid the perception that they are merely replacing one drug with another. However, it must be taken orally on a daily basis, making adherence a problem among all but the most committed patients. Cornish et al. (1997) randomly assigned federal probationers to a 6-month program of probation plus naltrexone and brief drug counseling or to probation plus counseling alone and found that opioid use was significantly lower in the naltrexone group, with the mean percent of opioid-positive urine tests among the naltrexone subjects at 8 % versus 30 % for control subjects ($p < 0.05$). Likewise 56 % of the controls and 26 % of the naltrexone group ($p < 0.05$) had their probation status revoked within the 6-month study period and were returned to prison. But treatment compliance was a problem, with only 52 % of subjects in the naltrexone group continuing for the 6-month duration of the study.

A depot formulation of naltrexone (e.g., Vivitrol®; approved in 2010 by the U.S. FDA for opioid addiction) addresses the problem of noncompliance with medication dosing, eliminates concerns about potential diversion (an issue with oral buprenorphine and take-home doses of methadone), and lessens the need for frequent patient presentation in the clinic or physician's office. Naltrexone injections reliably prevented relapse within 1 month after detoxification

(Foster et al. 2003), and multi-site research in Russia found Vivitrol effective for treating heroin addiction over 6 months (Krupitsky et al. 2011).

70.2.7 Managing Offenders Under Community Supervision

We have reviewed several prominent psychosocial and pharmacological treatment approaches used for drug-involved offenders. In addition to the specific treatments employed, it is important to consider how best to identify and manage these offenders to maximize accountability, compliance, and clinical progress. Two notable approaches are the drug court model and the application of testing and sanctions.

70.2.7.1 Drug Courts

There are currently more than 2,000 drug courts operating in the United States. Programs can also be found in Australia, Canada, the United Kingdom, and New Zealand. Drug courts vary in how they manage their caseloads, in the ancillary services they offer, and in the testing and sanction schedules they apply. What they all have in common is the provision of ongoing supervision from a judge, with offenders appearing before the judge for regularly scheduled updates. The drug court movement has been very successful. Many evaluations suggest that this is an effective approach to managing offenders in the community (Belenko 1998), though most of the support comes from non-randomized evaluations. The most rigorous evaluation, using a randomized, intent-to-treat design, was conducted on the Baltimore City Drug Court in Maryland (USA). A 1-year follow-up showed significantly lower levels of drug use and fewer arrests among those assigned to the drug court versus the control condition. By the time of the 3-year follow-up, these differences were no longer significant, although trends still favored the drug court participants (Gottfredson and Exum 2002; Gottfredson et al. 2005).

70.2.7.2 Testing and Sanctions

In 2004, a pilot program entitled Hawaii's Opportunity Probation with Enforcement (HOPE) was implemented in Honolulu in response to Judge Steven Alm's frustration with inept probation supervision, particularly in the management of methamphetamine abusers. Honolulu's probation officers were overwhelmed with high caseloads (often over 180:1), were struggling to manage their workloads, and were limited in their ability to detect and respond to violations. These difficulties led to long delays in responses to probation violations (positive urinalyses, missed appointments with probation officers, and missed treatment or failure to comply with drug treatment conditions) and high rates of noncompliance. The typical noncompliant offender would accumulate a long list of violations before action was taken. Under HOPE, offenders were given clear instructions on the content and implications of their community supervision, and the sentencing judge (or hearing officer) clearly laid out the rules of the

supervision program. Offenders who violated the terms of probation were immediately arrested and brought before a judge or hearing officer the same day. Under HOPE, *every* violation of community supervision terms was met with a sanction. *Parsimonious* use of punishment enhanced the legitimacy of the sanction package and reduced the frustrations and costs associated with tougher sentences, such as long prison stays. Results of a randomized evaluation of HOPE showed that drug use, missed appointments, and arrests for new charges in the year following randomization were reduced by one half to two thirds (Hawken and Kleiman 2009).

70.3 Conclusion

This chapter highlights the importance of capitalizing on the criminal justice system to identify and intervene with substance-misusing offenders. The high prevalence of use among offenders is a consistent international trend. Moreover, drug users in the criminal justice system pose risks to themselves and the general population through their commission of drug-related property and violent crime, as well as through the spread of infectious diseases, such as HIV and HCV.

Although the need for some level of intervention is clear, our review of existing treatment options and their supporting research underscores the fact that appropriate solutions are still not well established. Nor can we be certain of the extent to which reductions in substance use will produce commensurate reductions in criminal activity (aside from that inherent to illicit drug use itself).

We conclude this chapter with several recommendations for practice and research that we consider to be important next steps in advancing this literature.

70.3.1 Focus on Implementation

Over a decade ago, Gendreau and colleagues wrote that "of all the issues critical to the development of effective correctional treatment programs, program implementation has been relatively ignored" (Gendreau et al. 1999, p. 180). This observation is no less relevant today. Implementation fidelity is a challenge in any setting, but even more so under the auspices of a correctional system. This is because correctional administrators understandably focus their attention on the primary goals of keeping the general public safe from offenders and incarcerated offenders safe from each other. Successfully carrying out a rehabilitative agenda within these settings requires not only a knowledge of implementation science but also a practical understanding of how the criminal justice system works and why. Identifying effective practices that can be implemented for offenders – whether in custody or under community supervision – is only a first step that must be followed by research on how to encourage other correctional organizations to adopt such practices and how to ensure that the key elements in the original intervention are not lost or diluted in the process.

70.3.2 Need for More Randomized Trials

Selection bias and other less-obvious confounds have historically undermined confidence in evaluations of interventions for substance misusers, and conducting rigorous, randomized trials can be even more difficult in correctional settings, where there is an ongoing concern over disparate treatment of convicted offenders. Awareness of – and appreciation for – experimental research with offenders appears to be growing, however, with the number of published trials between 1982 and 2004 more than double that published in the two decades before (Farrington and Welsh 2005). Correctional research remains a challenge, but Asscher and colleagues (2007) have offered several useful suggestions based on their experiences conducting clinical trials with juvenile offenders in the Netherlands, including methods for overcoming institutional resistance, maintaining cooperation from study participants, and dealing with high staff turnover.

70.3.3 Clarify the Role of Coercion: When It Helps, When It Hurts

As we mentioned earlier in this chapter, reviews of the coerced treatment literature for substance-misusing offenders have not led to conclusive results (Wild et al. 2002). One important weakness of this body of research is that most studies of coerced treatment fail to measure this construct directly, but rather assume its presence given the nature of the criminal justice system. Because offenders who are mandated to participate in treatment can vary substantially in their perceived need for treatment, this methodological shortcoming obscures the extent to which coercion facilitates or undermines the therapeutic process. Another significant weakness is that the majority of coerced treatment studies rely on treatment retention or graduate rates as the outcome, rather than reductions in relapse and recidivism. The continued use of the criminal justice system as a setting for identifying substance misusers and mandating them to treatment should be accompanied by a more nuanced understanding of the effects of formal and informal sources of coercion.

70.3.4 Distinguishing "Addicted Offenders" from "Offender Addicts"

In most countries, the capacity for providing substance abuse treatment services in prison falls well short of the estimated need (Dolan et al. 2007). Absent a dramatic reversal of this trend, it is critical that researchers and practitioners develop criteria for determining which substance misusers are most likely to benefit from treatment and, among these, for whom reduced drug use will produce reduced criminal behavior.

Distinguishing offenders whose drug use impels criminal behavior from those whose drug use is merely coincidental has proven an elusive goal among addiction researchers and criminologists, but there is some evidence that such a distinction

can be made. For example, Nurco and colleagues (1988) classified 214 narcotic addicts according to their criminal involvement during a 2-year pre-addiction period and then compared rates of criminality during addiction periods for those who had engaged in crime prior to becoming addicted (approximately one half of the sample) and those who had not. As hypothesized, both groups increased their rates of criminality during high-addiction periods. However, during subsequent periods of low use, 78 % of the high-crime subjects (based on criminal activity during their pre-addiction period) continued to engage in criminal activity versus only 40 % of those in the low-crime group. Between-group differences were particularly disparate for drug dealing, with the high-crime group being responsible for 91 % of the drug-dealing crimes during the nonaddiction periods.

70.3.5 Examine the Use of Depot Medications for Opiate-Dependent Offenders

The high risk of death among offenders during the first 2 weeks following release from prison – and the fact that drug overdose is the leading cause (Binswanger et al. 2007) – suggests that drug use treatment might be considered effective even if it only reduced use or prevented relapse during the initial post-release phase. Newly approved depot formulations of naltrexone (e.g., Vivitrol®) and buprenorphine (e.g., Probuphine®) offer promise for overcoming poor medication adherence and eliminate the risk of these substances being diverted for recreational use. Moreover, even a single administration of these medications immediately prior to release from custody can reduce the threat of fatal opiate-related overdoses during the initial reentry period, when risks are at their highest. Given their promise, more evaluations of depot pharmacotherapies for released offenders are strongly recommended, particularly concerning strategies to encourage initial interest in these medications and to increase the percentage of offenders who return for subsequent doses.

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A Case Study from Egypt

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Tarek A. Gawad

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71.1 Introduction

The Middle East and North Africa (MENA) continues to be a region with limited data on the extent of the HIV problem. A 2010 review of evidence on HIV in the MENA region concluded that, while there was no evidence of an HIV epidemic, without an aggressive program of HIV prevention among high-risk groups, this situation could rapidly change for the worse (Abu-Radda et al. 2010). According to the Joint United Nations Programme on HIV/AIDS (UNAIDS 2012), the number of people newly infected with HIV in the MENA region increased by 35 % between 2001 and 2011. Consequently, efforts to identify high-risk groups and initiate HIV prevention methods are a priority in the region.

Egypt launched two national strategies in 2008, one on drug use and the other on HIV. Both strategies address the importance of prison inmates as a target population for intervention. In collaboration with the United Nations Office on Drugs and Crime (UNODC) Regional Office of the Middle East and North Africa (ROMENA) regional project on increasing access to drug use and HIV prevention and care services in prison settings, an interministerial national prison task force was

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formulated to coordinate activities aimed at reducing the negative social and health consequences of drug use in prisons. Accordingly, the prison task force has facilitated the implementation of an assessment of drug use and the HIV status of prisoners in six facilities in Egypt. These assessments are used to describe the need for HIV prevention in prison settings and, accordingly, provide the technical expertise and resources required to provide such.

The Egyptian Prison Authority called for a consultation meeting on October 2008 to present the concept of establishment of drug treatment facilities, rehabilitation programs, social reintegration, and vocational training for inmates within the prison premises. The main outcome of this consultation meeting was to conceptualize the prison initiative described below. Besides the prison authorities and UNODC ROMENA representatives, the steering committee permanent members were the Anti-Narcotics General Administration, the National Fund on Drug Use and Addiction, the Ministry of Health (General Secretariat for Mental Health and National AIDS Programme), the International Society of Addiction Medicine (ISAM), UNAIDS Country Office, and Egyptian academic institutions.

Upon recommendation from the members of the steering committee, a baseline study funded through UNODC ROMENA to assess the situation related to drug addiction and HIV infection in prisons and to provide necessary information for planning the best possible intervention was undertaken in 2009. This project aimed to provide specialized treatment and rehabilitation services to drug-dependent prison inmates while minimizing the negative health consequences of drug use within prison settings in Egypt. The project also sought to provide job opportunities for the targeted group of inmates during imprisonment and after release through the establishment of vocational workshops as part of rehabilitation and social reintegration.

71.2 The Survey

71.2.1 Survey of Drug Use in a Cairo Prison (From Ali Kabbash 2009)

One prison in the Cairo area was chosen to conduct a survey on drug use and HIV risk behavior. Individual interviews were conducted by experienced interviewers in a private setting. Participants were assured that their results would not be shared with the prison authorities. In addition to the individual interviews, focus groups of six to eight individuals were conducted. These focus groups included groups of inmates, guards, health-care workers, and social workers (different groups for each category). Data from the focus groups presented a consistent picture across categories. There was general agreement that there is a considerable amount of drugs in the prison and that they come into the prison in a variety of ways: family visits, prisoner trips outside the prison, and with food brought in by prison suppliers.

The quantitative survey study consisted of 1,926 participants, randomly selected, which represented 10 % of the prison population. The mean age of participants was 35 years, and 50 % were married; 36 % were illiterate, and 78 % were manual

laborers. The majority were imprisoned for drug and theft crimes (67.5 %), with sentences ranging from 1 to 10 years (69.9 %). Knowledge about HIV was variable, with 88 % and 82 % reporting that they knew that sexual behavior and sharing injection equipment were methods of HIV transmission, respectively, but only 59 % knew of mother-child transmission and 40 % thought HIV could be transmitted by insect bites. Eighty-nine percent (1,541) agreed to be tested for HIV, although only 43 % were aware there was treatment for HIV.

Fifty-three percent of participants reported that they knew of drug use in the prison, and 49.7 % of participants reported taking drugs in the prison. The majority of prisoners had a history of drug dependence before prison admission, with an average onset age of use of 18.6 ($SD = 5.37$) years. Drug injection had been practiced by 22 % of drug-dependent participants before prison, and 6.7 % reported injecting drugs in prison. The same syringe was generally shared by a group of persons and reused for several days. The common drugs are parkinol, other psychoactive pills, and hashish/bango. Sixty-five percent do not consider themselves to be dependent upon drugs, and 88 % reported they had never experienced withdrawal symptoms. Five percent of participants reported that they had overdosed from drugs, and 3.7 % reported more than one overdose episode. Fewer than 5 % had ever participated in treatment, and only 2.5 % felt they needed treatment in prison.

The combined efforts of the prison officials, the other Egyptian governmental and academic leaders, and the representatives of the UNODC ROMENA program have revealed evidence indicating considerable drug use in Egyptian prisons. The drug use and related behaviors (e.g., needle sharing and sex while under the influence of drugs) are reasons for concern about high-risk behaviors for HIV transmission within Egyptian prisons. According to UNAIDS (2012), new cases of HIV in Egypt are being reported at an increasing rate, and there are few HIV prevention activities in Egypt to address this public health problem. Although rates of HIV are believed to be low in Egypt, relative to other parts of the world, this situation could change rapidly if high-risk groups and high-risk settings are ignored. Clearly the prisons in Egypt are settings where the rates of HIV and the transmission of HIV are seriously elevated as compared to the general society.

Following the collection of the survey data presented above, there were discussions among Egyptian prison, health, and academic leaders about the most effective strategies for addressing the concerns about HIV transmission and drug use in Egyptian prisons. A plan was drafted to consider the development of addiction treatment and HIV prevention programs within Egyptian prison settings, combined with community aftercare to prevent relapse to drug use once individuals are released from prisons into the community. There was an extensive review of prison treatment and aftercare options from the literature around the world. Extensive discussions occurred regarding the possibility that this demonstrated need to address the Egyptian prison situation could be an excellent opportunity to conduct pilot programs in Egypt with addiction medications, including Suboxone® for opioid dependence. Further information is needed on the extent of opioid use in Egyptian prisons. If significant levels of opioid use are found, the induction and

treatment of opioid injectors with Suboxone within Egyptian prisons, along with their continuing treatment in the community provided by university hospital outpatient programs, could be an important innovation. Medication would be restricted to the prison settings and to the pharmacies of the university hospitals to protect against diversion of Suboxone onto the illicit market.

These very innovative and forward-thinking plans were interrupted by the political upheavals in Egypt in early 2011. The prison that was involved in the survey and was a site for the pilot project was severely impacted during the unrest of the "Arab Spring." Subsequently, there have been ongoing changes in government leadership in the prison and health sectors as the political leadership in Egypt has changed. As stability returns to Egypt, there is hope that these plans can be restarted as part of a responsible public health program.

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Drug Courts

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Douglas B. Marlowe

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Abstract

Drug courts provide judicially supervised substance abuse treatment in lieu of criminal prosecution or incarceration. Substantial research demonstrates that drug courts reduce crime, incarceration rates, and substance abuse, improve the psychosocial functioning of offenders, and produce positive cost benefits for taxpayers. Evidence has identified the optimal target population for drug courts and many of the best practices that are associated with improved outcomes in these programs. Although most of the research on drug courts has been conducted in the USA, emerging evidence is beginning to reveal positive benefits in European, Australasian, South American, and Caribbean countries as well. The challenge now is to extend the reach of drug courts without sacrificing their efficacy or safety.

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72.1 Introduction

Over 80 % of adult offenders in the USA misuse drugs or alcohol, meaning they were arrested for a drug- or alcohol-related offense, were intoxicated at the time of their offense, reported committing their offense to support a drug or alcohol problem or they have a significant history of substance abuse or substance abuse treatment (National Center on Addiction and Substance Abuse [NCASA] 2012). Approximately one quarter to one half of offenders are estimated to misuse drugs or alcohol in European, Australasian, South American, and Caribbean nations (Cooper et al. 2013). Providing substance abuse treatment can reduce recidivism rates substantially (Chandler et al. 2009); however less than one quarter of drug-involved offenders will complete a substance abuse treatment episode (Marlowe 2002).

Drug courts were created to improve offenders' compliance with substance abuse treatment. The drug court judge leads a multidisciplinary team of professionals that commonly includes representatives from the prosecution, defense bar, treatment agencies, case-management agency, probation department, and law enforcement. These team members meet frequently in staff meetings to review participants' progress in treatment and offer recommendations to the judge about potential consequences to impose (National Association of Drug Court Professionals [NADCP] 1997). The consequences may include rewards such as verbal praise, reduced supervision requirements, or small gifts; punitive sanctions such as verbal reprimands, writing assignments, community service, or brief intervals of jail detention; or adjustments to the participant's treatment regimen. The consequences are administered during regularly scheduled status hearings at which the judge discusses the matter with the participant in court. In pre-adjudication drug courts, the ultimate legal incentive is to have the criminal charge(s) dropped or withdrawn, and in post-adjudication drug courts, the legal incentive is to avoid a sentence of incarceration or reduce the length or conditions of probation.

The first drug court was founded in Miami/Dade County, Florida, in the USA in 1989. Currently, there are more than 2,700 drug courts in the USA (Huddleston and Marlowe 2011). Nearly 30 countries other than the USA have also established or are planning to establish drug courts, including Argentina, Australia, the Bahamas, Barbados, Belgium, Bermuda, Brazil, Canada, Cayman Islands, Chile, Columbia, Costa Rica, the Dominican Republic, El Salvador, England, Grenada, Ireland, Jamaica, Mexico, Norway, Panama, Peru, Scotland, Suriname, and Trinidad and Tobago (Cooper et al. in press).

In 1997, the National Association of Drug Court Professionals in the USA promulgated what are commonly referred to as the "10 Key Components" of drug courts (NADCP 1997). A few years later, the International Association of Drug Treatment Courts (IADTC) adopted the 10 Key Components but added three more components focusing on the social reintegration of participants, ensuring flexible treatment for indigenous populations and ethnic minorities, and planning for aftercare recovery services. The IADTC principles are embodied in a document entitled the *13 Key Principles for Court-Directed Treatment and Rehabilitation Programmes* ("13 Key Principles") [see Text Box].

International Association of Drug Treatment Courts (IADTC)
13 Key Principles for Court-Directed Treatment and Rehabilitation Programmes

1. The programmes integrate substance dependency treatment services with justice system case processing.
2. Using a non-adversarial approach, prosecution and defense lawyers promote public safety while protecting offenders' due process rights.
3. Eligible offenders are identified early and promptly integrated into the programme.
4. The programmes ensure access to a continuum of substance dependency treatment and other rehabilitation services.
5. Compliance is objectively monitored by frequent substance abuse testing.
6. A coordinated strategy governs responses of the court to programme non-compliance (and compliance) by offenders.
7. Ongoing judicial interaction with each offender in a programme is essential.
8. Monitoring and evaluation measure the achievement of programme goals and gauge effectiveness.
9. Continuing interdisciplinary education promotes effective planning, implementation, and operations of these court-directed programmes.
10. Forging partnerships among courts directing treatment programmes, public agencies, and community-based organizations generates local support and enhances programme effectiveness.
11. Ongoing case management includes the social support necessary to achieve social reintegration.
12. There is appropriate flexibility in adjusting programme content, including incentives and sanctions, to better achieve programme results with particular groups, such as women, indigenous people and minority ethnic groups.
13. Post treatment and after-care services should be established in order to enhance long term programme effects.

The success of adult drug courts (described below) has spawned an array of other types of problem-solving courts or treatment courts, including juvenile drug courts, family drug courts (for guardians in child abuse and neglect cases), driving while impaired (DWI) courts, mental health courts, and veterans treatment courts (for impaired military veterans). Considerably less research has been conducted on these newer models than on the original adult criminal model; however, emerging evidence suggests some of the newer programs are beginning to show favorable results. This chapter reviews the large body of research on adult criminal drug courts. The reader is referred to other sources for information on newer variants of the drug court model (Huddleston and Marlowe 2011; Marlowe 2011).

72.2 Effectiveness of Drug Courts

72.2.1 Criminal Recidivism

Meta-analyses are advanced statistical procedures that calculate the average effects of an intervention across numerous research studies. Several meta-analyses performed in the USA and Canada (Aos et al. 2006; Bhati et al. 2008; Downey and Roman 2010; Latimer et al. 2006; Lowenkamp et al. 2005; Mitchell et al. 2012; Shaffer 2010; Wilson et al. 2006) and a national multisite study in the USA (Rossman et al. 2011) concluded that drug courts significantly reduced criminal recidivism – typically measured by rearrest rates within 2 years of entry into the drug court – by an average of 8–14 %. In randomized controlled experiments, the reductions in recidivism were found to have lasted for at least 3 years postentry (Gottfredson et al. 2005; Mitchell et al. 2012; Turner et al. 1999), and in one study the effects lasted 14 years (Finigan et al. 2007).

A recent meta-analysis in the USA concluded that drug courts also significantly reduced incarceration rates by an average of 8–12 % (Sevigny et al. 2013). Notably, however, this impact did not translate into lesser use of jail or prison beds. Although the drug court participants were less likely to be incarcerated than comparable offenders charged with the same crimes, participants who were unsuccessfully terminated from the drug courts ultimately served more jail or prison time. In other words, the drug courts reduced the number of offenders who were sent to jail or prison but increased the length of the jail or prison sentences for the unsuccessfully terminated cases. The net result was that the unsuccessful cases washed out the effects of the successful cases, thus leading to a negligible impact on jail and prison resources.

This finding could be interpreted as an indictment of drug courts because they may not reduce jail or prison overcrowding or overreliance on the most expensive correctional resources. An alternative interpretation, however, is that drug courts reduce crime rates while having no impact on correctional populations or taxpayer expenditures. In other words, they achieve larger crime reductions than other correctional programs without increasing jail or prison censuses. Research does not, as yet, shed light on this debate. It is unknown whether crime rates would increase if drug courts reduced the consequences for unsuccessful termination. Some participants might be less likely to apply themselves in treatment if the consequences for failure were less severe, thus leading to higher termination rates or crime rates. Future research needs to address this important and policy-relevant question.

72.2.2 Cost-Effectiveness

In line with their positive effects on crime reduction, drug courts have also proven to be cost-effective. Meta-analyses of cost-effectiveness studies concluded that drug courts produced an average of approximately $2–2.25 in direct benefits to

the criminal justice system for every $1 invested (Bhati et al. 2008; Downey and Roman 2010; Rossman et al. 2011). These savings reflected measurable cost-offsets to the criminal justice system stemming from reduced rearrests, law enforcement contacts, court hearings, the use of jail or prison beds, and the tangible impacts of crime victimization. When more distal cost-offsets were also taken into account, such as savings from reduced child foster care placements and healthcare service utilization, studies have reported economic benefits ranging from approximately $4 to 27 for every $1 invested, resulting in savings to local communities of roughly $3,000–22,000 per participant (e.g., Aos et al. 2006; Finigan et al. 2007; Mayfield et al. 2013).

72.2.3 Psychosocial Outcomes

In 2005, the US Government Accountability Office (GAO 2005) concluded that drug courts significantly reduced criminal recidivism and saved money for taxpayers as a consequence of their impact on crime. However, the GAO also concluded that little was known about their effects on other important outcomes such as substance abuse, employment, family functioning, and mental health.

In response to the GAO report, the US National Institute of Justice (NIJ) funded a national study of adult drug courts entitled the Multisite Adult Drug Court Evaluation (MADCE; Rossman et al. 2011). The MADCE compared outcomes for participants in 23 drug courts located in seven geographic regions around the USA ($N = 1{,}156$) to those of matched comparison offenders drawn from six nondrug court sites in four geographic regions ($N = 625$). The participants were interviewed in person at entry and at 6- and 18-month follow-ups and provided oral fluid specimens at the 18-month follow-up.

In addition to reporting significantly less involvement in crime, the drug court participants also reported significantly less use of illicit drugs and heavy use of alcohol (defined as $\geq$4 drinks per day for women or $\geq$5 drinks per day for men) at the 6- and 18-month follow-ups. These self-report findings were confirmed by saliva drug tests which revealed significantly fewer positive results for the drug court participants at the 18-month assessment. The drug court participants also reported significantly greater improvements in their family relationships and non-significant trends favoring higher employment rates and school enrollment. These findings confirmed that drug courts produce psychosocial benefits for participants beyond crime reduction.

72.2.4 International Perspective

Rigorous studies in Australia (Jones 2013) and Canada (Somers et al. 2011) have demonstrated that drug courts can significantly reduce crime and produce cost benefits in those countries as well. In other nations, most drug courts are still in

the formative stages and efforts to evaluate their outcomes have only recently been initiated.

A 2010 survey conducted by American University on behalf of the Organization of American States (OAS) analyzed responses from drug court officials in several South American, Central American, and Caribbean nations (Cooper et al. 2010). The majority of the respondents reported that drug courts in their countries appeared to be reducing crime better than traditional correctional dispositions and approximately half of the respondents reported notable cost savings. Brazil, for example, reported 12 % recidivism for participants in its drug court in Rio de Janeiro as compared to a general recidivism rate of 80 % for nontreatment-oriented criminal dispositions. These figures are merely estimates but they do suggest that drug courts are feasible and potentially desirable to implement in South American and Caribbean nations.

72.3 Effective vs. Ineffective Drug Courts

Because meta-analyses calculate the *average* effects of an intervention, the results can mask substantial variability in the performance of individual programs. On the plus side, approximately three quarters (78 %) of the drug courts in the meta-analyses significantly reduced criminal recidivism (Shaffer 2006) with the best drug courts reducing recidivism by as much as 35 % (Lowenkamp et al. 2005; Shaffer 2006). These positive findings were, however, by no means universal. A substantial minority (22 %) of the drug courts were found to have had no impact on recidivism (Shaffer 2006), and in a few instances some drug courts were associated with increases in recidivism of as much as 15 % (Lowenkamp et al. 2005).

These findings underscore the importance of identifying the best practices in drug courts that minimize harms and optimize positive impacts. The critical task facing the drug court field is to determine what distinguishes effective drug courts from the ineffective or harmful ones. A substantial body of evidence is beginning to answer this important question. Studies reveal the poorest performing drug courts (1) targeted their services to the wrong types of drug-involved offenders, (2) delivered ineffective or contraindicated services, or (3) both.

72.3.1 Target Population

A growing body of research indicates which types of offenders are most in need of the full range of interventions embodied in drug courts. These are the offenders who are (1) addicted to or dependent on illicit drugs or alcohol and (2) at substantial risk for criminal recidivism or failure in less intensive rehabilitative dispositions. Drug courts that focus their efforts on these individuals – commonly referred to as high-need and high-risk offenders – reduce crime approximately twice as much as those serving less serious offenders and return approximately 50 % greater cost savings to

their communities (Bhati et al. 2008; Carey et al. 2012; Downey and Roman 2010; Lowenkamp et al. 2005).

These findings are consistent with a well-validated criminological theory called Risk-Needs-Responsivity (RNR). According to RNR, intensive programs such as drug courts offer the greatest benefits for high-risk offenders who have more severe antisocial propensities or treatment-refractory histories; however, such programs are often unnecessary or counterproductive for low-risk offenders (Andrews and Bonta 2010). High-risk offenders have a generally poor prognosis for success in standard treatment and often require intensive and sustained interventions to dislodge their entrenched, negative behavioral patterns. Low-risk offenders, in contrast, are less likely to be on a fixed antisocial trajectory and are apt to improve their conduct following a run-in with the law. Therefore, intensive interventions may offer small benefits for low-risk individuals but at a substantial cost (DeMatteo et al. 2006). Worse still, low-risk offenders may learn antisocial attitudes and behaviors from associating with high-risk offenders, which can make their outcomes worse. It has been found that providing formal substance abuse treatment for nonaddicted substance abusers can lead to higher rates of reoffending and a greater likelihood of those individuals becoming addicted (Lowenkamp and Latessa 2005; Wexler et al. 2004). This might be an unintended effect of exposing them to antisocial peers or interfering with their engagement in productive activities, such as work or school.

72.3.2 Best Practices

In fiscally challenging times, there is always the pressure to do more with less. This raises the question of whether certain components of the drug court model can be dropped or the dosage decreased without eroding the effects. The key components of drug courts are hypothesized to include an ongoing schedule of judicial status hearings, a multidisciplinary team approach to managing cases, a standardized regimen of evidence-based substance abuse treatment, frequent drug and alcohol testing, and contingent sanctions and incentives (NADCP 1997). Each of these hypothesized key components has been examined by researchers to determine whether it is required for effective results.

72.3.2.1 Judicial Status Hearings

Judicial status hearings are the defining ingredient of a drug court. Many correctional programs offer substance abuse treatment, urine drug testing, and sanctions and rewards for drug-involved offenders; however, only drug courts are led by a judge and require participants to appear frequently in court for status hearings. The evidence is exceptionally strong that judicial status hearings are a critical ingredient for effective outcomes in drug courts, assuming the programs are treating the appropriate target population of high-risk and high-need offenders.

A substantial body of research establishes the importance of scheduling status hearings no less frequently than every 2 weeks (biweekly) during the first phase of

a drug court. In a series of experiments, researchers randomly assigned drug court participants to appear before the judge every 2 weeks for status hearings or to be supervised instead by their clinical case managers and brought into court only in response to repetitive rule violations. The results revealed that high-risk participants had significantly better counseling attendance, drug abstinence, and graduation rates when they were required to appear before the judge every 2 weeks (Festinger et al. 2002). This finding was replicated in Australia (Jones 2013) and subsequently confirmed in a prospective matching study in which the participants were assigned at entry to biweekly hearings if they were assessed as being high risk (Marlowe et al. 2007).

Similarly, a meta-analysis involving 92 adult drug courts (Mitchell et al. 2012) and a multisite study of nearly 70 drug courts (Carey et al. 2012) reported significantly better outcomes for drug courts that scheduled their status hearings every 2 weeks during the first phase of the program. Scheduling status hearings at least once per month until the last phase of the program was also associated with significantly better outcomes and nearly three times greater cost savings (Carey et al. 2012).

Not surprising, outcomes are influenced not only by how often judges interact with participants but also by the length and quality of those interactions. Outcomes have been found to be significantly better when judges spent an average of at least 3 min, and as much as 7 min, interacting with the participants in court (Carey et al. 2012). Studies consistently find that drug court participants perceived the quality of their interactions with the judge to be among the most influential factors for success in the program (Goldkamp et al. 2002; National Institute of Justice [NIJ] 2006; Turner et al. 1999). The MADCE reported significantly greater reductions in crime and substance use for judges who were rated by independent observers as being more respectful, fair, attentive, enthusiastic, consistent, and caring in their interactions with participants in court (Rossman et al. 2011). Similarly, a statewide study in New York reported significantly better outcomes for judges who were perceived by the participants as being fair, sympathetic, caring, concerned, understanding, and open to learning about the disease of addiction (Farole and Cissner 2007). Outcomes were generally poor for judges who were perceived as being arbitrary, jumping to conclusions, or not giving participants an opportunity to explain their sides of the controversies.

A study of approximately 70 drug courts reported nearly three times greater cost savings and significantly lower recidivism when the judges presided over the drug courts for at least two consecutive years and thus had greater seniority and experience (Carey et al. 2012). Significantly larger reductions in crime were also found when the judges were assigned to the drug courts on a voluntary basis and their terms on the drug court bench were indefinite in duration. Evidence suggests most judges are less effective at reducing crime during their first year on the drug court bench than during ensuing years (Finigan et al. 2007). Presumably this is because judges, like most professionals, require time and experience to learn their jobs effectively. For this reason, drug courts that annually rotated their judicial assignments or had participants appear before alternating judges had the poorest outcomes

in several research studies (Finigan et al. 2007; NIJ 2006). Participants in drug courts often lead chaotic lives and require substantial structure and consistency to change their maladaptive behaviors. Unstable staffing patterns, particularly when they involve the central figure of the judge, are apt to exacerbate rather than ameliorate the disorganization in participants' lives.

72.3.2.2 Multidisciplinary Team

One of the more controversial features of drug courts is having professionals from different disciplines meet regularly to coordinate their functions as a team (NADCP 1997). Traditionally, judges, prosecutors, defense attorneys, and treatment providers did not sit down together to decide how best to respond to offenders' behaviors. This practice has raised concerns among some commentators about whether drug court professionals might be sacrificing their ethical obligations of neutrality, objectivity, confidentiality, or zealous representation. Although anecdotal arguments abound on both sides of the debate, no empirical evidence indicates whether such ethical concerns are justified.

Evidence is beginning to emerge to indicate whether a multidisciplinary team is necessary to improve outcomes. Research reveals the more effective drug courts do require ongoing attendance at staff meetings and status hearings by the judge, defense counsel, prosecutor, treatment providers, and law enforcement (Carey et al. 2012). When any one of these professional disciplines was absent regularly from team discussions, the programs had outcomes that were, on average, approximately 50 % less favorable. In other words, if any one professional discipline walks away from the table, there is reason to anticipate the effectiveness of a drug court could be reduced by as much as one half.

Studies indicate the drug court judge, in particular, should attend pre-court staff meetings regularly (Carey et al. 2012). The staff meeting is where team members share their observations and impressions about participants' performance and propose consequences for the judge to consider. The judge's presence at the staff meeting ensures that each team member's perspective is taken into account when important decisions are made. Observational studies have revealed that when judges did not attend pre-court staff meetings, they were unlikely to be adequately informed or prepared when they interacted with the participants in court (Portillo et al. 2013).

72.3.2.3 Substance Abuse Treatment

Substance abuse treatment forms the heart of a drug court program. The basic assumption underlying drug courts is that addiction is fueling or exacerbating criminal activity. Therefore, it is hypothesized to be necessary to treat this disorder in order to reduce crime and improve the psychosocial functioning of offenders (NADCP 1997).

Early studies did not cast a favorable light on the quality of substance abuse treatment in drug courts. Treatment services in several US drug courts were characterized as being nonevidence based, lacking in a coherent focus or structure,

and delivered by inadequately trained staff. The services also tended to be indistinguishable from those routinely offered to noncriminal justice populations and thus might not have adequately addressed the unique needs and risk factors presented by offenders.

Recent studies provide a more informative and sanguine picture of the impact of substance abuse treatment on drug court outcomes. The success of drug courts appears to be attributable, at least in part, to the fact that they significantly increased participants' exposure to substance abuse treatment. The longer drug court participants remained in treatment and the more sessions they attended, the better were their outcomes (Gottfredson et al. 2007; Peters et al. 2002; Shaffer 2010).

Outcomes are also significantly better in drug courts that offer a continuum of care for substance abuse treatment which includes residential treatment and recovery housing in addition to outpatient services (Carey et al. 2012; Koob et al. 2011). The best results are achieved when participants are required to meet with a treatment provider or clinical case manager for at least one individual session per week during the first phase of the program (Carey et al. 2012; Rossman et al. 2011). Many participants are unstable clinically and in a state of crisis when they first enter a drug court, and group sessions might not provide adequate time or opportunities to address each participant's clinical and social service needs. Individual sessions may reduce the likelihood that participants will fall through the cracks during the early stages of treatment when they are most vulnerable to cravings, withdrawal symptoms, and relapse.

Better results have been reported in drug courts that developed specialized therapy groups for participants with specific clinical needs or demographic characteristics, such as women with trauma histories (Messina et al. 2012) and young African-American male participants (Vito and Tewksbury 1998). Young African-American males have commonly expressed dissatisfaction with group-based services in drug courts; therefore, it may be especially important to develop effective and culturally tailored services for this demographic group.

A substantial body of research spanning several decades reveals that outcomes from correctional rehabilitation are significantly better when (1) the offenders received behavioral or cognitive-behavioral treatment (CBT) interventions, (2) the interventions were carefully documented in treatment manuals, (3) the treatment providers were trained to deliver the interventions reliably according to the manual, and (4) fidelity to the treatment model was maintained through continuous supervision of the treatment providers (Andrews and Bonta 2010). Adherence to these same principles has been associated with significantly better outcomes in drug courts (Gutierrez and Bourgon 2012). Examples of manualized CBT curricula that have been shown to reduce criminal recidivism in adult drug courts include Moral Reconation Therapy (MRT) (Cheesman and Kunkel 2012) and the MATRIX Model (Marinelli-Casey et al. 2008).

Finally, research reveals outcomes were better for drug courts that contracted with a single coordinating agency to serve as the primary case manager for treatment services (Carey et al. 2012). The coordinating agencies did not

necessarily provide all of the clinical services, but they were responsible for assessing the participants, referring them to the appropriate treatment programs, and providing routine progress reports to the judge and drug court team. It can be exceedingly difficult to stay abreast of participants' progress when they have been referred to numerous treatment providers. Designating a primary case manager to coordinate the referrals appears to be essential for maintaining an accurate flow of up-to-date information and administering consistent and timely consequences for participants' performance in treatment.

72.3.2.4 Medically Assisted Treatment

Medically assisted treatment (MAT) can significantly improve outcomes for addicted offenders (NCASA 2012). Buprenorphine or methadone maintenance administered prior to and immediately after release from jail or prison has been shown to significantly increase opiate-addicted inmates' engagement in treatment; reduce illicit opiate use; reduce rearrests, technical parole violations, and reincarceration rates; and reduce mortality and hepatitis C infections (Chandler et al. 2009). These medications are referred to as agonists or partial agonists because they stimulate the central nervous system (CNS) via a comparable neural mechanism as illicit drugs. Because they can be addictive and may produce euphoria in non-tolerant individuals, they may be resisted by some criminal justice professionals.

Positive outcomes have also been reported for antagonist medications such as naltrexone which are nonaddictive and nonintoxicating. Naltrexone blocks the effects of opiates and partially blocks the effects of alcohol without producing psychoactive effects of its own. Two small-scale, open-label studies reported better outcomes in drug courts for alcohol-dependent participants receiving an injected form of naltrexone called Vivitrol (Finigan et al. 2011).

A recent national survey found that nearly half of US drug courts do not use medications in their programs (Matusow et al. 2013). One of the primary barriers to using medications was a lack of awareness of or familiarity with medical treatments. For this reason, the NADCP Board of Directors issued a unanimous resolution directing drug courts in the USA to learn the facts about MAT and obtain expert consultation from duly trained addiction psychiatrists or addiction physicians.

72.3.2.5 Drug and Alcohol Testing

The success of any drug court depends on the reliable monitoring of participants' behaviors. If the drug court team does not have accurate information about whether participants are being compliant or noncompliant in the program, there is no way to apply incentives or sanctions correctly or to adjust treatment and supervision services accordingly.

The most effective drug courts perform urine drug testing at least twice per week during the first several months of the program (Carey et al. 2012). Because the metabolites of most commonly abused drugs are detectable in human bodily fluids for only about 1–4 days, testing less frequently leaves an unacceptable time gap during which participants can abuse substances and evade detection.

In addition, drug testing is most effective when it is performed on a random basis. If participants know in advance when they will be drug tested, they can adjust the timing of their usage accordingly or take other countermeasures, such as frontloading on water, to elude the tests.

Although urine testing is the most common testing procedure in drug courts, other technologies which extend the time window for detection are becoming commonplace. The Secure Continuous Remote Alcohol Monitor (SCRAM) is an anklet-monitoring device that detects alcohol vapor in sweat and transmits a signal wirelessly to a remote monitoring station. Research suggests SCRAM monitoring can be effective at deterring alcohol consumption among recidivist offenders in drug courts when it is worn for at least 90 consecutive days (Flango and Cheesman 2009). Similarly, ethyl glucuronide (EtG) and ethyl sulfate (EtS) testing extend the time window for detection of alcohol metabolites from a few hours to several days. At least one randomized controlled trial has reported improved outcomes when a drug court used EtG/EtS testing (Gibbs and Wakefield 2014).

72.3.2.6 Graduated Sanctions and Rewards

Drug courts administer gradually escalating sanctions for infractions and rewards for accomplishments (NADCP 1997). The nearly unanimous perception of staff members and participants is that sanctions and incentives are strong motivators of behavioral change in drug courts (Lindquist et al. 2006; Goldkamp et al. 2002). Two randomized controlled experiments confirmed that administering gradually escalating sanctions for positive drug tests and other infractions significantly reduced substance use and crime among drug-involved offenders (Harrell et al. 1999; Hawken and Kleiman 2009).

The use of jail sanctions is highly controversial in drug courts. Although some commentators have theorized that the realistic threat of a jail sanction provides the necessary leverage for drug courts to retain recalcitrant offenders in treatment, research on this issue is sparse for understandable reasons. It is very difficult, if not impossible, to study the question in a controlled experiment. Few participants, staff members, or research ethics boards would permit jail to be imposed in a nonindividualized and randomized manner.

The most practical way to study this issue is to compare outcomes between similarly matched drug court participants who did or did not face the realistic possibility of receiving a jail sanction. So far, such studies have yielded mixed findings. One study reported better outcomes when drug court participants faced a realistic prospect of jail (Carey et al. 2008) whereas another study found no differences in outcomes regardless of whether jail could be imposed (Hepburn and Harvey 2007). Another practical method for addressing this question is to interview the drug court participants themselves. A consistent finding from focus-group studies is that drug court participants viewed the threat of jail to be a highly motivating factor that kept them engaged in treatment and committed to their sobriety (Goldkamp et al. 2002; Farole and Cissner 2007).

At least two randomized experiments investigated the effects of enhancing the positive rewards that were available to participants for desired achievements in

drug courts (Marlowe et al. 2008; Prendergast et al. 2008). The rewards were delivered in the form of payment vouchers or gift certificates for negative urine tests and other desired accomplishments. Neither study found improved outcomes apparently due to a statistical ceiling effect. The outcomes were so favorable in both of the drug courts that it was difficult to improve any further upon those outcomes. In one of the studies, however, a preplanned interaction analysis revealed a nonsignificant trend ($p = .08$) in which high-risk offenders with more serious criminal histories performed relatively better in the enhanced reward conditions (Marlowe et al. 2008). This preliminary finding might suggest that when drug courts treat the most incorrigible drug offenders, tangible rewards may make additive contributions to outcomes. More research is needed to confirm and explain this interaction effect.

72.3.3 International Perspective

As was mentioned earlier, research on drug courts is just starting to be implemented in countries other than the USA. No studies have been published that have addressed the appropriate target population or best practices for drug courts in other countries. It does appear that the average risk and need level for drug court participants may be substantially higher in some other countries. Much of the increase in the US arrestee population has been fueled by drug-possession cases, and in some US jurisdictions offenders can be sentenced to jail or prison for simple drug possession. Because drug possession is less likely to receive an incarcerative sentence in many European and South American nations, drug courts in those countries are apt to treat offenders having more serious criminal charges and addiction backgrounds. Future studies should address this question and determine whether offenders' risk and need levels influence drug court outcomes in other countries.

Virtually all of the countries surveyed by American University reported that they were providing services in their drug courts consistent with the 10 Key Components or the 13 Key Principles. It appears that many international drug courts are exporting the model from the USA largely as it was designed and with relatively modest adaptations. Future research will hopefully reveal what changes, if any, may be required to adapt the drug court model to the needs and traditions of other countries and peoples.

72.4 Conclusion

Despite their unquestionable efficacy, drug courts in the USA serve only a small fraction (about 5–10 %) of the roughly 1.5 million adults arrested each year who meet criteria for substance abuse or dependence (Bhati et al. 2008). The primary obstacle to expanding the reach of drug courts in the USA is a lack of funding and not an absence of judicial interest or public support (Huddleston and Marlowe 2011). Convincing lawmakers that they will recoup their investments and reap

substantial economic gains by investing in drug courts is now a primary goal of rational drug policy in the USA.

Other countries seeking to extend the reach of drug courts will almost certainly face comparable challenges. The American University survey identified a number of barriers to implementing drug courts that were reported by several countries. The most frequently reported barriers were a lack of adequate funding (especially for treatment services), high rates of staff turnover, an underappreciation for the serious problems faced by participants, inadequate services for teens and young adults, and an insufficient availability of adjunctive services such as childcare and vocational training (Cooper et al. 2010). These barriers are virtually identical to those reported in the USA and do not appear to reflect unique problems encountered by Latin-American or Caribbean nations.

The major challenge for all nations is to extend the reach of drug courts without diluting the intervention below effective levels. Any program can be made cheaper simply by lowering the dosage and providing fewer services to more participants. The difficult task is to maintain effectiveness in the process. Many interventions show efficacy on a small scale only to have the quality of implementation drift unacceptably downward as they are applied on a large scale in day-to-day practice.

The big question is whether the criminal justice systems in various countries will move in the indicated direction. Facing huge budget deficits, some governments are imposing across-the-board funding cuts to correctional and treatment programs. There is no need to speculate about the likely effects of such actions. If history is a guide, any cost savings that might be realized in the short term will shift the financial burden to a later date as the result of increased crime, drug abuse, and related impairments. The appropriate course of action is to shift funds away from costly and ineffective programs, such as prison, to those that are proven to reduce crime and conserve public resources. Rather than taking an "axe" to cost-effective programs, policymakers should reallocate funds away from inefficient programs, reinvest them in evidence-based programs, and return the net cost savings to taxpayers. Much is possible if lawmakers apply what works rather than what is expedient, comfortable, or popular. If lawmakers do not rise to this challenge, then all of the research in the world will have little impact on public health or public safety.

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Trauma and Addiction Medicine

73

Michael Dinh and Matthew Oliver

Contents

Abstract

Injuries represent a major burden of illness across the world, and injuries are disproportionately represented amongst those with concurrent *addiction disorders*. In this patient population, various behavioral, mental state, social, and clinical factors conspire to increase the risk of injury-related harms, ranging from road crashes due to drink driving to interpersonal violence and self-harm behaviors as a result of acute behavioral disturbance. *Trauma-related presentations* to the emergency department in drug-affected patients therefore represent some of the most dramatic clinical scenarios in acute medicine. Not only are there injury-related management issues, but also clinical concerns related to drug intoxication and the possibility of withdrawal syndromes masking serious injury. This brief chapter highlights these considerations in this complex group of patients and outlines a structured clinical approach in the *emergency department*.

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73.1 Introduction

Injuries remain the leading cause of death around the world in people under 45 years of age (Krug et al. 2000). It is estimated that over 16,000 people die every day from injuries and many more are left with permanent disabilities. As a result of increased urbanization and road transportation in developing countries over the past 20 years, road trauma is projected to rise to the fifth most common cause of death by 2020 (WHO 2013). In recognition of this, the World Health Organization set out to reverse this trend by supporting a global decade of action on improving road safety from 2011 to 2020. Disturbingly, intentional or self-inflicted injuries follow closely behind road trauma as a cause of death in these age groups and, as the population ages, particularly in developed nations, falls have become an increasingly common cause of morbidity in the elderly (Stevens et al. 2006).

Substance abuse, particularly alcohol, has long been recognized as a risk factor for injury (Cherpitel et al. 2005; WHO Department of Mental Health and Substance Abuse 2004). Causal associations exist on a number of levels. Firstly, there are dose-related effects of certain drugs ranging from disinhibition and impaired concentration to aggression and impaired level of consciousness that increase the risk of road crashes, falls, and assaults (Australian Institute of Health and Welfare 2011). Secondly, social factors related to the acquisition and distribution of illicit drug use increase exposure to violent crime and penetrating trauma. Thirdly, substance abuse often coexists with or results in psychiatric disorders, increasing the risk of self-inflicted harm and harm to others (Cunningham et al. 2003). Finally, major trauma is a well-described risk factor for the development of post-traumatic stress disorder, which itself leads to substance abuse and a vicious cycle of further injury (Yehuda 2002). For these reasons and more, substance abuse exacts an enormous cost to society. In Australia in 2009, the costs of alcohol abuse alone were estimated to be over $15 billion dollars, which include tangible costs such as costs of road trauma, hospital treatment, and crime and intangible costs such as lost productivity and emotional distress (Laslett et al. 2010).

Emergency departments (ED) function within health systems to triage, identify and stabilize acute undifferentiated health problems (Schuur and Venkatesh 2012). This paradigm is exemplified by the modern trauma system, where the trauma team assesses and manages patients with life-threatening injuries with the ED and prepares the patient for definitive surgical treatment. EDs are also an important point of episodic health care for many people through unplanned admissions and exacerbations of chronic conditions. In most societies EDs also provide access to basic level care and a safety net for socially disadvantaged and isolated populations. Therefore, EDs commonly identify and treat patients with substance abuse disorders ranging from simple to complex conditions (McGeary and French 2000).

As such patients present to ED with a wide spectrum of problems, some of which are listed in Table 73.1. The effect of alcohol and drugs of addiction on a patient's cognition and physical abilities means that these patients are at a higher likelihood

Table 73.1 Common emergency presentations for patients with substance abuse

Drug intoxication or overdose
Drug withdrawal syndromes
Seeking help or counseling regarding substance abuse
Injuries
Blunt and penetrating assault
Road traumas (including motor vehicle, pedestrian, cyclist)
Falls
Domestic violence
Self-inflicted harm
Behavioral and mental state disturbance
Aggression and violence
Psychosis
Depression
Confusion
Medical conditions
Liver failure
Hyponatremia
Renal failure
Cardiac failure
Atrial fibrillation
Stroke
Aortic dissection
Sepsis
Pneumonia
Infective endocarditis

of suffering trauma. A study in Louisiana found that up to 70 % of patients admitted after severe injuries had positive drug or ethanol urine screens (Madan et al. 1999). A similar study of over 1,000 trauma patients at the R Adams Cowley Shock Trauma Center found that rates of positive drug screen around 64 % (opiates, cocaine, and marijuana) in trauma patients (Soderstrom et al. 1997). Patients with substance abuse disorders often present with multiple complaints, confounding even the simplest presentations like a sprained ankle and making such patients amongst the most complex patients to deal with safely and successfully in the ED environment. These management difficulties are often compounded by a patient's own impaired judgment and increased risk-taking behaviors (Field et al. 2001). As a consequence the severity of injury and the likelihood of suffering trauma tend to be higher in acutely intoxicated individuals than the general population (Waller et al. 1986; Rivara et al. 1993; Soderstrom et al. 1997). Despite these increased chances of trauma, the evidence that these patients have a worse outcome compared

Table 73.2 Risk behaviors found of acute and chronic alcohol users

Behavior	Percentage of patients ($n = 145$)
Driving	
Do not always wear seat belt	37.9 %
Do not always obey speed limit	71.1 %
Ridden with driver under the influence	41.1 %
Driving under the influence	33.8 %
Additional driving	
Recent citation/arrest/license suspension	44.1 %
Prior DWI/DUI arrest	17.2 %
Violence	
Carried a weapon	10.3 %
Recent physical altercation	35.2 %
Prior assault with weapon	30.3 %
Suicide	
Suicidal ideation in last year	26.9 %
Prior suicide attempt	13.8 %
Additional risk factors	
Lifetime drug use	57.9 %
Current drug use	32.5 %
Prior alcohol/drug treatment	20.0 %

Table adapted from Field et al. (2001)
DWI driving while intoxicated, *DUI* driving under the influence

to nonintoxicated patients is sparse. Only a handful of studies demonstrate worse outcomes for drug and alcohol-intoxicated patients compared to nonintoxicated patients with the same injuries (Chen et al. 1999; Tulloh and Collopy 1994; Swanson et al. 2007; Dischinger et al. 2001; Hadjizacharia et al. 2011) (Table 73.2).

As a consequence this population is at an increased risk of motor vehicle accidents (MVAs), pedestrian injuries, blunt assault, penetrating assault (stab wound or gunshot wound), self-harm, and falls (Savola et al. 2005; Demetriades et al. 2004). One study reviewing the odds of patients suffering from severe injury following an MVA identified alcohol use as the greatest predictor over other factors such as age, seat belt use, and vehicle crash. The presence of alcohol intoxication more than doubled the risk for serious injury (Waller et al. 1986).

73.1.1 Injury Profiles

A variety of injury profiles are found in drug and alcohol users ranging from minor to major injuries depending on the mechanism. Minor injuries may include

orthopedic injuries such as ankle sprains or rib fractures, minor burns, or soft tissue injuries. Although not requiring operative intervention in the majority of cases, minor injuries still account for a large burden on emergency department resources (London et al. 2009; Tominaga et al. 2004). Conversely major injuries, such as severe head injuries, and multisystem trauma require intensive care, operating rooms, and rehabilitation care which explains the high cost of these patients to the healthcare system (Moore 2005; Lucas 2005).

73.2 Clinical Aspects of Trauma

73.2.1 Clinical Considerations

73.2.1.1 Initial Assessment and Management

When patients arrive at trauma centers, an initial assessment of patient's injuries is made concurrently with initial interventions. Most centers follow an Advanced Trauma Life Support (ATLS) structure, whereby evaluations of a patient's Airway, Breathing, Circulation, and Neurological state (ABCs) form part of the "primary survey" (ATLS Subcommittee, American College of Surgeons' Committee on Trauma, and the International ATLS working group 2013). If a life-threatening abnormality is detected during assessment of these areas, then necessary interventions such as airway intubation and intravenous fluid resuscitation are commenced immediately. These are usually undertaken in the context of a distressed patient with limited corroborative history or available information about medical or social background. Following on from this, a "secondary survey" is commenced whereby a more complete medical history is obtained and the patient examined systematically to detect any other significant injuries. Further investigations often include radiographs, computed tomography (CT), and focused abdominal sonography in trauma (FAST). Many of these processes occur simultaneously by numerous clinicians working in a resuscitation or trauma team.

A number of variables dictate a patient's disposition and treatment in the emergency setting. For example, if a patient is severely injured and has tachycardia and hypotension, then they will often be treated presumptively for hemorrhagic shock with blood product transfusion and consideration for urgent operative intervention. However, similar injuries without clinical evidence of ongoing hemorrhage may not require urgent operative intervention and may simply require observation. Another example may be the patient with a head injury and a normal Glasgow Coma Scale (GCS) of 15 who may not require further urgent management. However, a head-injured patient with reduced conscious level, i.e., GCS < 9, or evidence of cerebral agitation (e.g., vomiting, confusion, or seizures) may require emergent airway intubation, urgent cranial CT, and craniotomy if there is evidence of intracranial hematoma.

Case Scenario
A 24-year-old male presents to an inner city emergency department with head and chest injuries following an assault in which he was beaten about the head with a baseball bat and stabbed with a small knife. He has a history of alcohol and cannabis use. He admits to injecting "ice" prior to the incident. He does not have family and frequently presents to this emergency department where he is well known for being disruptive and aggressive towards the nursing staff. On presentation he is sweaty and agitated and has a Glasgow Coma Score of 13, a heart rate of 130, and a blood pressure of 90/50. He has multiple facial abrasions, a large occipital scalp hematoma, and a small 2 cm penetrating wound to his left upper chest. The patient becomes violent and demands to leave the emergency department stating that there are people out to "get him."

73.2.1.2 Acute Physiological Changes Related to Drugs and Alcohol

As shown in Table 73.3 there are a number of affects from alcohol and drugs that make standard assessment and management of an intoxicated patient a clinical challenge. The main areas of concern specific to these individuals are (i) hemodynamic status and (ii) neurological status.

Hemodynamic Status

Nearly all drug and alcohol use can affect blood pressure or pulse as shown in Table 73.3. The most concerning presentation to any physician managing trauma

Table 73.3 Physiological effects of common drugs and alcohol

	Cardiovascular affects	Respiratory affects	Neurological affects
Alcohol	Peripheral vasodilation	Respiratory depression	Reduced conscious level and airway compromise, disinhibition
	Increased risk of arrhythmias	Reduced pulmonary clearance	
	Myocardial dysfunction	Higher incidence of pneumonia	
		Reduced pulmonary vascular resistance	
Stimulants, e.g., cocaine, methamphetamine, MDMA ecstasy	Tachycardia, hypertension, vasoconstriction, arrhythmias, myocardial ischemia	Increased respiratory rate	Agitation, aggression, anxiety, delirium, seizures
Sedatives/ depressants, benzodiazepines, opiates, marijuana	Increased systemic vascular resistance	Reduced respiratory drive with opiate used	Depressed conscious level, confusion, psychosis

patients in general is hemorrhage. Signs of hemorrhage in nonintoxicated adult may include increased respiratory rate, tachycardia, peripheral vasoconstriction, anxiety, and, later on, hypotension. Patients therefore intoxicated with any of the common substances of abuse could fit any of these criteria at any one time. Animal models have demonstrated the increased likelihood of bleeding with alcohol intoxication (MOSS et al. 1960; Zink et al. 1998; Blomqvist et al. 1987; Brackett et al. 1994; McDonough et al. 2002), most likely due to the inability to cause peripheral vasoconstriction to shunt blood to vital areas such as the heart, lungs, and brain. Stimulant-affected patients such as cocaine or methamphetamine users are typically tachycardic and agitated, giving the appearance of someone who is in hypovolemic shock. As a consequence not only is the patient's ability to cope with blood loss affected but also the assessment by treating physicians may be confounded. Drug-affected patients are therefore more likely to get over-investigated due to the concern for missing potentially life-threatening injuries not detected on routine assessment. However, the converse could be true in that physicians may be tempted to attribute exam findings and vital signs to drug intoxication and potentially miss life-threatening injuries, resulting in delays to definitive care and misdiagnosis. This has large implications for health-care resources because as blood transfusion requirements are increased, rates of CT scanning increased resulting in longer inpatient length of stays (Swanson et al. 2007; Moore 2005; Lucas 2005).

Neurological Status

Most drug abuse syndromes have potentially significant effects on cognitive function. The primary difficulty with any drug-intoxicated patient therefore is the assessment of the cognitive state and whether this is due to the intoxication or traumatic brain injury (TBI). Any unconscious patient (GCS < 9) requires urgent airway intubation and mechanical ventilation to prevent the occurrence of gastric aspiration and prevent secondary brain injury. Previous evidence has demonstrated that alcohol-intoxicated patients are more than twice as likely to require airway intubation compared to nonintoxicated patients with head injury (Gurney et al. 1992). Due to the alteration in cognitive level including aggression, agitation, and sedation, intoxicated patients with evidence of head injury or involved in serious mechanisms of injury are more likely to undergo CT scanning (Moore 2005). Also due to the inability to perform an adequate physical exam, patients are more likely to require imaging of multiple body areas for evaluation (Roudsari et al. 2012). Part of this imaging will frequently require not only cranial CT but also CT scans of the cervical spine. Well-described criteria are used in trauma patients to evaluate for cervical spine injury; however, patients must be alert and nonintoxicated to meet criteria for cervical spine clearance (Hoffman et al. 1998; Mower et al. 2004). Patients failing the criteria typically require CT cervical spine imaging with evidence of head injury or concerning mechanism of injury.

73.2.1.3 Chronic Physiological Affects of Drugs and Alcohol

Intravenous drug use has a number of implications for acute injury management particularly in relation to difficult intravenous access (Lucas 2005). However, chronic alcohol use is associated with a much more serious problem of coagulopathy and bone marrow suppression making hemorrhage control more problematic. The liver is responsible for the production of clotting factors II, VII, IX, and X as well as other components, all of which form essential elements of the coagulation cascade. Chronic alcohol users have reduced hepatic synthetic function, and therefore, production of these clotting factors is reduced. Normal patients suffering trauma are at an increased risk of bleeding from a variety of mechanisms (Brohi et al. 2003), and those patients with a pre-morbid reduction in clotting activity therefore have an increased risk of hemorrhage and death. Chronic alcohol use also impairs the immune response, and subsequently these patients are at increased risk of post-injury sepsis, acute respiratory distress syndrome (ARDS), and multiple organ failure (MOF) (Moore 2005).

Patients chronically abusing analgesic-related medications such as oxycodone, codeine and oral morphine, as well as illicit narcotics may require higher doses of analgesia due to tolerance and dependence. This creates significant challenges to health-care workers caring for patients in the acute care setting. Physicians need to be aware of the risks of under- and overtreating patients in this situation, and a multidisciplinary approach should be taken with early intervention from drug and alcohol specialists. Patients with alcohol dependence are also at serious risks of withdrawal and as a consequence are at risk of a myriad of signs and symptoms such as seizures, nausea, vomiting, abdominal pain, and diaphoresis. Treating physicians need to be vigilant to this condition and take appropriate steps to prevent withdrawal features while excluding other trauma-related complications such as sepsis, raised intracranial pressure, and ongoing hemorrhagic shock.

73.2.2 Emergency Department Considerations

73.2.2.1 Behavioral Management

Patients experiencing the acute effects of illicit drugs particularly methamphetamines are at risk of violent or aggressive behavior, requiring behavioral control in ED (Swanson et al. 2007; Latt et al. 2011; Degenhardt et al. 2007; Van der Swan et al. 2011). Measures include various de-escalation strategies, physical restraints, chemical sedation, and seclusion. The most appropriate strategy is usually one which allows safe and thorough clinical assessment while minimizing the risk of over-sedation and the complications associated with it, such as apnoea and hypotension. Restraint and sedation strategies should be consistent with local and institutional policies.

73.2.2.2 Mental Health Assessment

Patients with self-inflicted physical injuries can range from superficial lacerations to gun trauma and attempted hangings. Concurrent drug ingestion is common in

these presentations. Patients with acute substance use like cannabis or amphetamines may also express ongoing thoughts of self-harm or hallucinations. A mental state assessment should be made in the acute setting to diagnose the presence of an acute mental health disorder and determine the need to detain a patient for ongoing psychiatric care. This becomes a critical decision when a patient with a possible serious injury requests to leave against medical advice (see case scenario). If the patient has a potentially life-threatening condition and the patient's capacity to make an informed decision is impaired, then a patient may be detained for treatment necessary to preserve life and immediate well-being under the common law principal of duty of care (Wand and Wand 2013). In this context, a patient who is mentally disordered due to acute drug ingestion should not be released until the person is deemed to be capable of making an informed choice and potentially life-threatening injuries have been assessed for and excluded.

73.2.2.3 Social Problems

Patients with substance abuse disorders often access EDs due to poor social supports or financial difficulties (McGeary and French 2000). In addition family members, partners, or children of individuals with substance abuse disorders may also present with injuries as a result of interpersonal violence. It is important for EDs to have screening tools for these conditions as many jurisdictions have mandatory reporting requirements for suspected domestic violence and child abuse.

73.2.2.4 Security

Security personnel are often available in EDs to assist in the management of violent behavior. Additional staff are often required to ensure patient safety by preventing them from absconding or to monitor and prevent harmful behaviors such as further self-inflicted harm while in ED. Patients presenting with gun-related injuries, particularly gang-related crime, should be managed as a potential security threat, and patients and visitors should be searched for potential weapons. The police should be notified if the clinician has reason to believe that a patient is in possession of a firearm and poses an ongoing risk to self or others.

73.2.2.5 Emergency Department Overcrowding

One of the most important challenges currently facing emergency departments around the world is overcrowding (Richardson and Mountain 2009). Lack of staffing and beds required to meet the demands of the health-care system means that many EDs are chronically overcrowded with patients. The main manifestations are longer waiting times and reduced efficiency and patient safety. In this often chaotic environment, patients with substance abuse disorders particularly those with behavioral or mental health problems are more likely to escalate to violent or aggressive behavior. Some emergency departments have implemented models of care that involve dedicated mental health and drug and alcohol clinicians in an attempt to meet the demands of these patients at an earlier stage of management in ED.

73.2.2.6 Screening and Brief Intervention

Although systematic reviews have confirmed the effectiveness of screening and brief alcohol intervention in the primary care setting, it is difficult to extrapolate these to the emergency setting for trauma patients. Acute distress due to a combination of injuries, mental health disorders, and toxicological effects, in addition to the environmental considerations outlined above, make brief intervention less likely to be effective in this context. Indeed a meta-analysis of brief alcohol intervention in EDs highlighted the heterogeneity of studies giving rise to conflicting results (Havard et al. 2008). Nevertheless, given the frequency at which patients with substance abuse disorders present to ED and the ability to connect a patient with the direct consequences of their substance use, screening and brief intervention in ED would appear to be at least an initial opportunity to discuss these issues with the patient and lend itself to other opportunities such as follow-up referrals to specialized drug and alcohol services.

Level one trauma center hospitals (those accredited to manage the most severe trauma patients) in the United States are now required by the American College of Surgeons to have an alcohol screening and brief intervention program for patients admitted under trauma. Few studies have investigated the effect of brief interventions in this context, and ones that have are limited by low follow-up rates (50–70 %). Screening and brief intervention within trauma inpatient units offer a number of advantages to the ED setting, namely, the more controlled environment where injuries have been definitively treated, concomitant effects of drug intoxication have cleared, and the patient being more likely to be cooperative.

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Mandatory Versus Voluntary Treatment and Rehabilitation of People Abusing Drugs: Initiatives from Malaysia

74

Mahmood Nazar Mohamed and Sabitha Marican

Contents

Abstract

Compulsory Centers for Drug Users (CCDU) were established in many countries to address the issue of drugaddiction such as drug treatment and rehabilitation center, drug detention center, drug prison, and others. Here, drug users were called inmates, were sent for mandatory treatment, and were subjected to "boot camp" approach with emphasis on discipline, religious values, social acceptable behavior, and punishment like canning. Little medical attention was given to these inmates and many contracted communicable diseases such as hepatitis, STIs, HIV, and tuberculosis while in mandated detention. Living conditions in very tight living quarters in these detention centers were very poor. As an

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alternative to compulsory drug detention and rehabilitation centers, the UN agencies and entities that are signatories to the Joint Statement that called for the closure of drug detention centers advocated for states to make available voluntary treatment, evidence-informed, and rights-based health and social services in the community. Several agencies especially under UNODC provide data, evidences, training, workshops, conferences, sponsored visitations to alternative sites, and consultations to target countries in order to reduce the number of CCDUs and to introduce a proper evidenced and outcome-based drug treatment and rehabilitation center. In Malaysia, the government set up an innovative project to harmonize the country's drug laws, addressing the CCDUs and human rights issue. The Cure and Care (C&C) project was established in 2010 in response to low treatment outcome such as high-relapse rates, poor reemployment capacities, and reengagement to criminal behavior associated with CCDUs. They began gradually to move away from CCDU and introduced a number of evidence and community-based treatment (CBTx) services for illicit drug users. Since then, Malaysia has made considerable progress in the provision of voluntary drug treatment and rehabilitation. This chapter discussed several challenges faced by countries that still practice CCDU and the success of some states that has introduced evidence and outcome-based drug treatment and rehabilitation center.

74.1 Introduction

Drug treatment and rehabilitation is one of the major inputs to the demand reduction strategy which is endorsed by the United Nations Office of Drug and Crime (UNODC) to reduce the burden of drug on its users and the society at large. The nature of the addiction disease requires people dependent to drugs to be treated and rehabilitated and later to be reintegrated back into society (Mahmood 2005). However, often enough as observed in the Asian countries, the method of drug treatment do not follow the science of what is evidenced and what is not. Many operate on the assumption that any treatment for drug addiction is better than no treatment, which is not true at all (Simpson et al. 1997). Many treatment programs in Asian countries prescribed to local norms, religious, spiritual, and the punitive discipline-based methodologies to "treat" drug addicts (Mahmood et al. 2006). Drug laws were enacted to contain the epidemic of drug addiction in their countries. People tested for drugs and found positive are taken in for mandatory treatment in government-operated treatment facilities. As such, human rights issues are often infringed (Tongue and Turner 1988; UNODC 2010c). This chapter looks at the shift from the mandatory to voluntary treatment of drug dependents and how innovative projects undertaken in the Asian countries have been made models for other countries to replicate.

74.2 Drug Use, Treatment and Rehabilitation

74.2.1 The Extent of Drug Use

The United Nations Office on Drug and Crime (UNODC) reported that in the year 2011, between 167 and 315 million people aged between 15 and 64 were estimated to have used an illicit substance in the preceding year, which is between 3.6 % and 6.9 % of the global adult population. Since 2008, there has been an overall 18 % increase in the estimated total number of people who had used an illicit substance in the preceding year, which to some extent reflects both an increase in the global population and a slight increase in the prevalence of illicit drug use. This implies that there is now more need, if not demand, for drug and substance addiction treatment and rehabilitation globally (WDR 2013).

Asia is one region that has been hardest hit by problematic drug use (APAIC 2013). There is an estimated of 25–40 % of all illicit drug users worldwide, as well as 60 % of opiate users and between 30 % and 60 % of ATS users coming from this region (WDR 2013). Data from Pakistan and China indicated an increase in the use of all types of drugs.

In 2012, Pakistan reported cannabis as the most commonly used drug, with an annual prevalence of 3.6 %, followed by prescription opioids (1.5 %) and tranquilizers and sedatives (1.4 %). Use of ATS (0.1 %) and cocaine (0.01 %) appeared to be low but emerging in this country (WDR 2013). The number of people addicted to drugs is also on the rise. At present, 5.8 % of the adult population, which is approximately 6.4 million persons or one in every 27 persons in Pakistan, is using drugs, while nearly 25 % of the youth population is involved in some form of drug abuse (Muhammad Qasim 2013).

In China, opioid use remains high. The number of registered heroin users is increasing each year. There were 1.24 million in 2011, compared with 1.06 million in 2010 (WDR 2013). There is a wide difference between the country's number of registered addicts (e.g., 900,000 in 2007) with an estimate of 12 million drug addicts (Michels et al. 2007). The number and proportion of registered users of ATS are also increasing (38 % of all registered users in 2012, compared with 28 % in 2010). In addition, there has been a major increase in the number of drug users registered for use of other substances, such as ketamine. In 2012, more than 7 % of registered drug users were using ketamine.

There are various forms of drug treatment facilities that have been reported for China. For example, in 2000, there were 717 compulsory detoxification units (CDU) with 105,529 beds, 69 work education units (WEU) with 52,598 beds, and 119 voluntary units with 7,020 beds. In 2006, a total of 377,000 drug addicts were detoxified and treated in these facilities, and only 9.5 % of this number is receiving MMT, while 4.3 % are from voluntary units (Michels et al. 2007).

Data from East and Southeast Asia reported higher levels of ATS use in 2011. DAINAP reports ATS use, in particular methamphetamine, continues to increase in most countries in East and Southeast Asia (APAIC 2013). The illicit manufacture of

ATS continues at high levels in the region. Methamphetamine seizures also remained high in 2011. Ecstasy has been in decline in recent years, but there are signs at the global level that the "ecstasy" market is recovering (APAIC 2013). The demand for specific ATS-related abuse treatment is at its peak; however, not many countries other than Japan, the Philippines, and Thailand are able to provide effective hospital-based treatment. Many countries in this region treated ATS abusers the same as opiate and marijuana users, thus lacking in treatment efficacy.

Ketamine use also remained widespread in some countries in the region and was reported in Brunei Darussalam, China, Indonesia, Malaysia, and Singapore. A recent study in Hong Kong of 97 drug users, most of whom primarily took ketamine, found that over 60 % of them suffered depression, 31 % complained of poor concentration, and 23 % had memory problems. This adds new dimension to substance abuse treatment in Asia especially for the younger age group (Tan Ee Lyn 2009).

To curb the growing problem with drug use and abuse, most countries in Asia enforced the supply and demand reduction strategies. Many also has prescribed to harm reduction strategies specifically opioids replacement therapies and needle and syringe exchange programs. However, with the existence of drug laws, mandatory (i.e., legally enforced) treatment for drug and/or alcohol abuse is being enforced in many Asian countries. Court-mandated alternatives to incarceration are still not available in many countries. Even in countries like Malaysia and Singapore which is considered to have departed from the more traditional "boot camp" drug treatment program, till to date, there are no legal provisions for a drug user to be mandated to MMT program.

74.2.2 Compulsory Center for Drug Users (CCDU)

The existence of CCDU has been observed in many countries since the onset of drug problem in this region. In the 1970s, CCDU is probably the only available facility used under the demand reduction strategy in the Asian countries albeit some treatment conducted in hospitals and medical clinics. In Southeast Asia countries, various forms of CCDU take place such as drug treatment and rehabilitation center, drug detention center, drug prison, and many more. Frequently, "boot camp" modality is used with emphasis on discipline, religious values, social acceptable behavior, and punishment like canning and chaining. Drug users mandated for drug treatment were often labeled as inmates. Little medical attention was given to these "inmates," and many contracted communicable diseases such as hepatitis, STIs, HIV, tuberculosis, and others as a result of their drug use, injecting drugs, multiple sexual partners, and, on top of that, poor living condition and very tight living quarters in the detention centers (Fu et al. 2012).

At present, over 300,000 men, women, and children suspected of using drugs are detained in some 1,000 compulsory centers for drug users (CCDUs) in East and Southeast Asia alone (UNODC 2012b). A large number of drug dependents were registered at CCDU because most often they were legally mandated by drug

(or antidrug) laws in their country to undergo treatment here. Almost all of these CCDUs are free or the parents have to pay a minimal fee for treatment and rehabilitation as compared to receiving treatment in hospitals and voluntary units or private treatment centers. As a point of comparison, in Malaysia, private treatment at private centers costs between 300 and 3,000 USD dollars; in Indonesia, it is between 250 and 5,000 USD; in the Philippines, it costs between 600 and 8,000 USD; and in Thailand, it is between 500 and 5,000 USD as compared to government CCDU which is generally free of charge (Mahmood et al. 2006). However, many drug dependents receiving treatment at CCDU reported being beaten, abused, raped, locked, chained, and treated like criminals. Followings are some testimonies by former detainees of drug treatment centers in China, Vietnam, Lao PDR, and Cambodia:

> If we opposed the staff they beat us with a one-meter, six-sided wooden truncheon. Detainees had the bones in their arms and legs broken. This was normal life inside. – Former detainee, Ho Chi Minh City, Vietnam, 2010 (UNODC 2011a).
>
> They try to teach not to use drugs, that it isn't good to use [drugs], while showing that normal people have a good future. I don't think the classes helped me stop using drugs... Some people use more drugs when they come out of Somsanga. – Former detainee, Vientiane, Lao PDR, late 2010 (UNODC 2012a).
>
> There are lots of people and not enough food. It was hard to sleep there because in my room there were 60 people. There was not enough water for the showers, only a few minutes to shower every day. – Former detainee, Vientiane, Lao PDR, late 2010 (UNODC 2011b).
>
> I tried to run away, and in the process, I broke both feet. When I went to the hospital for treatment, I was arrested and sent back to the drug addiction center... Inside I was given very little food, and they never gave me any medicine at all to treat my feet. I was locked up for about half a year and my feet became crippled. – Written account from former detainee, Yunnan, China, 2009 (UNODC 2012a).
>
> All drug detention must work. We get up at five in the morning to make shoes. We work all day and into the night. That's all it is. – Former detainee, Yunnan, China, 2009 (UNODC 2010a).
>
> There were about seven children in my room but maybe about 100 children altogether. The youngest was about 7 years old. The children are not drug users but homeless, like beggars on the street. – Former detainee, Vientiane, Lao PDR, late 2010 (UNODC 2011b).
>
> [A staff member] would use the cable to beat people...On each whip the person's skin would come off and stick on the cable... – Former detainee, age 16, describing whippings he witnessed in the Social Affairs Youth Rehabilitation Center in Choam Chao, Cambodia (UNODC 2010b).

The situation of CCDU in East and Southeast Asia was reviewed at the first Regional Consultation for Drug Users, organized by UNODC Regional Centre for East Asia and the Pacific, ESCAP, and UNAIDS Regional Support Team in December 2010 in Thailand. On March 9, 2012, a Joint Statement was issued by 12 United Nations agencies, including the UN Office on Drugs and Crime (UNODC), the World Health Organization (WHO), the UN Children's Fund (UNICEF), and UNAIDS, calling for the closure of drug detention centers and the release of the people detained there "without delay" (UNOCD 2012b).

This UN Joint Statement highlights the concerns associated with the CCDUs, including increased vulnerability to HIV and tuberculosis infection as well as

insufficient legal safeguards and judicial review. Detention of people in such centers has also been reported to involve a range of other measures that violate human rights, including substandard conditions, forced labor, physical and sexual violence, and lack of access to health care, including HIV prevention services, among others (UNODC 2012b).

As an alternative to compulsory drug detention and rehabilitation centers, the UN agencies and entities that are signatories to the Joint Statement advocate for states to make available voluntary, evidence-informed, and rights-based health and social services in the community. Several agencies especially under UNODC such as TREATNET, DAINAP, and APAIC provide data, evidences, training, workshops, conferences, sponsor visitations to alternative sites, and consultations to target countries in order to reduce the number of CCDU and to introduce a proper evidence-based and outcome-based drug treatment and rehabilitation center.

74.2.3 Human Rights and Alternatives to Drug Treatment

Throughout the Asian region, there are a plethora of concerns about human rights violations; forced labor; physical and sexual violence; substandard living conditions; a lack of access to health care (Fu et al. 2012); ineffective, nonevidence-based treatment modalities (Noor Zurina et al. 2012); and an increasing awareness that CCDUs fail to address drug use as a chronic relapsing health disorder (Mahmood and Dzahir 2007; UNODC 2010c). Relapse rates among these "inmates" are high, and drug use occurs as immediately as they were released from the detention centers. At this juncture, many treatment experts want the government to make it a priority to end these abuses and redirect their support to voluntary, community-based treatment and other programs that truly respect drug users' human rights. This has led many governments to look at evidence- and rights-based alternatives to CCDUs (UNODC 2012b).

Harm reduction was introduced in the Asian countries before the turn of the millennium when a number of countries are facing epidemic numbers of HIV infections (Mahmood 2005). Many opposed the idea of substitution therapy and needle exchange because of religious values and beliefs that giving needles and syringes will not help drug addicts to stay off drugs (Mahmood and Dzahir 2007). In Malaysia, harm reduction strategies were endorsed by the government in 2001, and by 2005, many of the strategies has been implemented with good success. These set of strategies were also widespread in other Asian and ASEAN countries with strong support from UNODC (Mahmood and Dzahir 2007; Mahmood 2010; UNODC 2013).

Other pertinent issues faced by Asian countries are the well-established drug control and fast emerging drug laws for mandatory treatment and rehabilitation. In Malaysia, the government set up an innovative project to harmonize between the country's drug laws, addressing the CCDUs and human rights issue (Mahmood 2011). The Cure and Care project was established in 2010 in response to low treatment outcome such as high-relapse rates, poor reemployment capacities, and

reengagement to criminal behavior associated with CCDUs. Here, the government, through the National Anti-Drug Agency (NADA), began gradually to move away from CCDUs and introduced a number of evidence- and community-based treatment (CBTx) services for illicit drug users. Since then, Malaysia has made considerable progress in the provision of voluntary drug treatment and rehabilitation (Mahmood 2012; UNODC 2013).

The statistics related to mandatory treatment in Malaysia is also evident to these new initiatives. The number of drug addicts caught under the Drug Dependent Act 1983 (Treatment & Rehabilitation) peaks at 38,672 in the year 2004; 97 % were male and 64.1 % are of the Malay ethnic origin. At this time, drug treatment and rehabilitation is mostly conducted at government CCDUs, also known as "Pusat Serenti" for a period not less than 2 years. Voluntary treatment centers are still very limited, and many do not practice evidence-based drug treatment. In 2008, the government permits the prescription of MMT by private medical practitioners for treatment of opiate dependents. Many came forward to pay for the treatment, ranging between 10 and 25 USD per treatment. In addition the Ministry of Health dispensed free methadone through NADA. As a result, the number of drug dependents arrested in 2010 decreased to 23,642. Then, in 2010, the Malaysian government initiated the Cure and Care project, which is a voluntary drug treatment clinic-based program, and the number caught in 2011 and 2012 reduced to, respectively, 11,154 and 9,015 (Mahmood 2012; NADA 2013).

The pioneering Cure and Care (C&C) clinic in Kuala Lumpur was the first to be set up by NADA in 2010 in response to the growing drug problem. The C&C clinic represents a shift in Malaysia's approach to drug treatment and a move away from institutionalized punitive rehabilitation. It offers non-court-mandated voluntary treatment program for drug users and addicts with no question asked for them to access to drug treatment and rehabilitation and health and psychosocial services free of charge.

At about the same time, the Cure and Care Service Centre (CCSC) was established with its first establishment in the drug-stricken area of Chow Kit Kuala Lumpur. CCSC provides the community-based treatment (CBTx) and gives basic support services such as food for the day and a place to rest, clean, bathe, and wash clothes. It also functions as an outreach center, providing counseling, medical checkups, psychosocial programs, methadone maintenance therapy, spiritual and moral education, and support for integration. About 100–150 clients visited CCSC Chow Kit daily; and over a span of 1 year, more than 200 were referred to the C&C clinics for treatment, and more than 500 gets referral to the methadone program at hospitals in Kuala Lumpur. Additional NGO-operated CCSC were also set up in the city of Ipoh and the rural area at Jengka Pahang to address to many drug dependents and IDUs who need to access to such services.

Under these initiatives, the Malaysian Government did not change its drug laws. The Drug Dependent Act (Treatment and Rehabilitation) (1983) is still being used to arrest drug addicts, but as shown in the above statistics, the number has been reduced over the years. The current UNODC-endorsed initiatives operate within the existing legal framework; they developed an open system with community-based

services and comprehensive interagency collaboration. This is one of the drug treatment and rehabilitation models in Asian countries acknowledged by UNODC to be considered as applicable in countries with strict laws on drugs but with much interest in human rights and public health (UNODC 2013).

74.3 Conclusion

In conclusion, UNODC has reported some positive efforts taken by many countries in the Asian region to depart from the traditional boot camp drug treatment modality to a more evidence-based substance abuse treatment. Countries like Malaysia, Thailand, and the Philippines have made tremendous effort to introduce MMT and other opiate substitution available for heroin abusers; however, no substitution is currently available for the ever popular ATS in the region. Many Asian countries like Afghanistan, Brunei, Cambodia, China, Iran, Laos, Pakistan, and Vietnam are studying efforts taken by Malaysia to harmonize between its strict drug laws and the humane, voluntary-based drug treatment program for drug users (NADA 2013). Positive responses and outcome of the C&C projects are being documented for the benefit of countries who wish to replicate the project for its own high-risk population.

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Opportunities for Addiction Service System Development: Case Studies from Vietnam, Lebanon and United Arab Emirates

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Contents

Abstract

In the twenty-first century, the development of addiction treatment services around the world has been increasingly guided by science and the use of evidence-based practices. This advancement can be seen in the three very different examples of Vietnam, Lebanon, and Abu Dhabi. Since 2008, the government of Vietnam, together with substantial support from international donors and technical experts, has established a network of over 60 methadone treatment programs, distributed

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around the country, to reduce the use of injected heroin and the related transmission of HIV. In Lebanon, a group of clinicians, with support from international organizations and a receptive government, have introduced buprenorphine into use for the treatment of opioid dependence. In Abu Dhabi, a concerted effort has been undertaken by the national government to build a comprehensive continuum of services, including addiction medications and evidence-based behavioral services, resulting in a fivefold increase in patients treated from 2009 to 2012. Despite substantial differences in the circumstances that generated these initiatives and their varying scope of services, the common theme across these efforts has been the implementation of science-based approaches with demonstrated effectiveness. The application of these effective strategies will provide a strong rationale and increase support for a public health approach to addressing drug abuse and addiction.

75.1 Introduction

Drug abuse and addiction "treatment" services began in many societies as part of their criminal justice system, social services system, community-based self-help efforts, or some combination of all three. The initial efforts to develop "treatments" for addicted individuals were frequently unclear about what they were treating. Was drug addiction a moral problem or a medical problem? Were addicted individuals bad people, weak in character, or sick people, with a medical/psychiatric condition? Among the factors that have spurred societies to develop drug treatment services are concerns about the following: drug-related crime, drug injection-related infectious diseases (e.g., HIV, hepatitis C), loss of work productivity, and the disruption caused to family members and communities (National Center on Addiction and Substance Abuse [NCASA] 2005; National Drug Intelligence Center [NDIC] 2011; UNDCP 1995). In many societies, the first response to drug use has been a public safety response addressing drug-related crime, including criminal penalties for drug possession and use (Chandler et al. 2009). A variation of incarceration in some societies is mandatory commitment in psychiatric institutions. Initial treatment alternatives to incarceration or commitment have typically been a patchwork of storefront counseling centers, therapeutic communities, sober living houses, self-help programs, and medical treatments for overdose and withdrawal. Part of the reason for this haphazard societal response has been that the fundamental nature of addiction was poorly understood, and even if it was viewed as a health problem or disease, there were no identified medical paradigms to treat this disease.

One thing was consistent across all parts of the world – until the late twentieth century, the initial treatment services for drug abuse and addiction had very little foundation in scientific research about addiction or evidence-based medicine. By the late twentieth century, the role of injection drug use in the AIDS pandemic stimulated, in some parts of the world, the interest of global public health leaders in efficient and effective evidence-based treatments for heroin use. The documented efficacy of methadone in decreasing injection drug use and reducing transmission of HIV has clearly been a major factor endorsing the implementation of methadone treatment services. To a lesser extent, the widespread increase in use of cocaine and

amphetamine-type stimulants (ATS) in many parts of the world has also increased interest in behavioral treatment approaches for individuals with psychostimulant disorders, whose psychotic and violent behavior can cause a serious detrimental effect on individuals and communities (UNODC 2013).

To further the global awareness of addiction science, the US National Institute on Drug Abuse (NIDA) initiated an international program in the early 1990s that has played a major role in engaging international investigators and institutions in addiction research and has served as a vehicle for the dissemination of addiction science. NIDA has sponsored and cosponsored dozens of international conferences and training events over the past 20 years to increase awareness of addiction science and its application. In addition, from 1990 through July 2013, NIDA has sponsored 408 international fellows from 103 countries for training fellowships via the NIH Humphrey program, the NIDA INVEST program, and other such programs (NIDA 2013). Further, NIDA has established seven binational agreements with other countries to promote co-funding of research and has added an international satellite meeting to its annual College on Problems of Drug Dependence (CPDD) meeting. This CPDD international satellite meeting has shown tremendous growth from a meeting of 20–25 participants at the first meeting in 2000, to a meeting of 300 enrollees from over 40 countries in 2013 (S.W. Gust, personal communication).

Another contributing factor to dissemination of addiction science is the establishment of the International Society of Addiction Medicine (ISAM), which developed from a small forum of MDs interested in addiction, to a large annual meeting of 400–500 participants. The latest developments in the field, with an emphasis on clinical applications of addiction medicine, are reflected in the annual ISAM meeting agenda. Finally, the World Health Organization (WHO) and United Nations Office on Drugs and Crime (UNODC) have been active contributors to the dissemination of addiction science. The UNODC Treatnet Program, initiated in 2007, has been incorporated into a joint WHO-UNODC effort to provide training and technical assistance internationally to regions developing treatment and harm reduction services. The Treatnet curriculum was created with an emphasis on science-based knowledge and evidence-based practices at its core (Tomás-Rosselló et al. 2010). As of 2013, over 1,200 individuals have been trained as trainers and 9,000 clinicians have received training via Treatnet (Saenz et al. 2015; UNODC 2007).

75.2 The Changing Face of Substance Abuse Treatment in Vietnam, Lebanon, and United Arab Emirates

75.2.1 Case Studies

The following international case studies provide examples of successful and diverse advancements in addiction treatment and public health service that were driven by the best scientific evidence, multiagency international collaborative efforts, and the influence of public health leaders and committed service providers with a vision for the future.

75.2.1.1 Vietnam

Vietnam, a country of 90 million people, has a significant prevalence of drug use and HIV. Injected heroin became a significant public health problem from the time of the war with the United States in the 1970s. In 1993, the government of Vietnam opened compulsory centers (06 centers), where drug users were reeducated, punished, and rehabilitated, since addicts were viewed as a "social evil." The 06 centers were part of a policy toward drug users in which drug users could be arrested and, without due process, immediately transported to the 06 centers, where they were routinely held involuntarily for 2 years; repeat offenders were held for even longer periods. While in the 06 centers, there was no identifiable drug treatment, and the primary activity was long hours of tedious manual labor. Although the 06 centers were not called jails, they were far more oriented to punishment and control than to medical or psychiatric treatment.

The first case of HIV infection was detected in Vietnam in 1990; by 1999, there were 17,046 diagnosed cases of HIV infection. By 2012, the estimated number of HIV-infected individuals was estimated at 206,887. Studies over this time period suggest that injection drug use (IDU) was the likely route of HIV transmission in 85–90 % of HIV-positive individuals. As of 2012, there were an estimated 220,000 injection drug users in Vietnam (Vietnam Ministry of Health 2012). Following passage in 2006 of the Law on HIV/AIDS Prevention and Control (known as the "HIV law"), the Vietnamese government, led by the Deputy Prime Minister, initiated a plan to change the focus of the response to the IDU/heroin problem in Vietnam. The Ministry of Health, with support from UNODC, WHO, Global Fund, USAID, Family Health International, and the United States President's Emergency Plan for AIDS Relief (PEPFAR), began plans to introduce methadone into Vietnam.

Methadone treatment programs were piloted in 2008 in Hai Phong and Ho Chi Minh City as a result of the 2006 HIV law. These pilot programs operated under guidelines developed by Vietnamese leaders and with extensive consultation from international experts. The guidelines were grounded in the best scientific evidence, and an extensive training program was implemented by local and international clinical experts to promote development of a methadone treatment system based on best practices. With the success of the pilot programs, the government decided to scale-up methadone programs in other provinces (Vuong et al. 2011). By July, 2013, 14,000 patients were in methadone treatment in 62 clinics in 20 Vietnamese provinces. The Ministry of Health (MOH) has projected that methadone treatment will be provided to about 80,000 drug users in 2015.

Studies on the outcomes of the methadone implementation in Vietnam have demonstrated promising results. In a four-site cohort study of 965 heroin users who started treatment in 2009, 88.3 % were retained in methadone treatment for 12 months (U.S. Agency for International Development 2011). Heroin use, as measured by urinalyses, was reduced from 100 % positive at admission to 21 % positive at 60 days in treatment; and over the subsequent 10 months, rates varied from 17 % to 10 % positive. Other study results indicated substantial reductions in injection drug use and crime, as well as improvements in mental health and quality of life.

If the Ministry of Health succeeds in its planned service development, Vietnam will have gone from two pilot project clinics in 2008 to treating over 80,000 patients with methadone in 2015 (Nguyen et al. 2012). This extraordinary expansion of treatment capacity brings with it huge challenges of service funding and workforce development. In 2011, Hanoi Medical University, in collaboration with UCLA, established an Addiction Technology Transfer Center to lead efforts to train clinical staff for the clinics being developed. Compounding the challenges, amphetamine-type stimulants (ATS) consumption has rapidly increased in Vietnam – 1.5 % of drug users in Vietnam in 2001 used ATS, whereas 6.5 % did in 2012 (Department for Social Evils Prevention [DSEP] 1995–2012). In order to address this emerging problem, training programs in motivational interviewing and the Matrix Model of treatment have been initiated to provide services to address the needs of treatment-seeking ATS users. In less than a decade, Vietnam has mounted a major public health effort to address the problems of drug use and HIV, and the policies that have guided this system development have been firmly grounded in addiction science.

The development of the Vietnamese treatment system and capacity-building effort has been the result of well-informed and responsive public health officials in the Vietnamese government, in cooperation with international funding organizations and technical assistance. The urgency for developing these services has been accomplished in parallel with an equally impressive HIV testing and treatment program. The challenge for the next decade will be to continue the expansion of the services to provide treatment access for all individuals who need them, to maintain the quality of the services, and to better integrate addiction services with HIV services and the larger health-care system. The development of addiction services in Vietnam over the past decade was an impressive exercise in public health service development, guided by the best scientific evidence and implemented by a multiagency international collaborative effort.

75.2.1.2 Lebanon

At the start of the twenty-first century, services for the treatment of substance use disorders in Lebanon were a collection of faith-based therapeutic communities and a limited set of treatment services from psychiatrists and psychiatric hospitals. Although these resources were helpful to patients and communities, there was no organized outpatient treatment and no use of addiction medications. In 2003, an organization named Skoun was created to deliver high-quality, evidence-based outpatient addiction services. Heroin addiction was the primary drug problem that was not being effectively addressed by existing treatment services. Skoun initiated their treatment services using a combination of harm reduction strategies, together with cognitive behavioral therapy (CBT), motivational interviewing, and psychiatric treatment. It was clear to Skoun staff from the beginning that to effectively engage and treat individuals addicted to opiates using a harm reduction philosophy, they would need addiction medications as part of their services. Therefore, an initial question was whether to introduce methadone or buprenorphine into Lebanon, where, to date, no medication-assisted treatment had been available. As they

reviewed practices associated with methadone and buprenorphine in Europe and the United States, they decided that the clinical data on the efficacy of buprenorphine and flexibility in its dosing and service delivery logistics made buprenorphine the preferable agonist medication to bring to Lebanon. Furthermore, in their initial discussions with the Ministry of Health, there were some concerns about methadone diversion, but there was general support for the idea of buprenorphine. However, because rates of HIV are low in Lebanon, there was no perceived public health urgency for addressing the injection drug use problem as there was in Vietnam, China, and countries in Eastern Europe.

Because there are close historical and cultural ties between Lebanon and France, it was not uncommon for opiate-addicted individuals from Lebanon to go to France to receive buprenorphine and return to Lebanon to participate in counseling treatment services at Skoun. As this practice developed and some pharmacies in Beirut established relationships with French pharmacies, buprenorphine became available, in a limited manner, for patients at Skoun. From 2005 to 2011, several hundred patients were treated with buprenorphine in Lebanon. During this period, discussions continued with government officials about the clinical effectiveness of buprenorphine and its value in improving the lives of addicted individuals. The Pompidou Group, UNODC, and the WHO Eastern Mediterranean office (EMRO) played important roles in hosting meetings to promote discussions of the use of buprenorphine in Lebanon and arranging visits for Ministry of Health officials to France and Iran to visit treatment centers using medications to treat opiate addiction. The persistent advocacy and encouragement by individuals at Skoun, along with other addiction and public health leaders in Lebanon and representatives of international organizations, resulted in official governmental approval for the importation and use of buprenorphine for the treatment of opiate addiction in February 2012.

During the first year since the passage of the approval of buprenorphine in Lebanon, 690 cumulative patients have been treated with buprenorphine, with the majority being in Beirut. Skoun has expanded services from its original clinic in Eastern Beirut to a second clinic in South Beirut, sponsored by the Drosos Foundation, a Swiss organization. This clinic, which was projected to enroll 75 individuals on buprenorphine in its first year, was met with tremendous demand for services and enrolled double that number (150) in its first 9 months of operation. In addition to the buprenorphine services provided at Skoun, a total of 45 psychiatrists have been registered by the Ministry of Health to prescribe buprenorphine. The use of buprenorphine in Lebanon is currently limited by a somewhat restricted distribution system (all medication has to be dispensed from two government hospitals in Beirut), and all buprenorphine is available only through patient fees, which are several hundred US dollars per month. Currently there are efforts to work with the government to promote treatment (including treatment with buprenorphine) in place of incarceration for drug offenders. Although the law to allow treatment rather than incarceration has been in place for almost a decade, it has not been implemented. The availability and effectiveness of buprenorphine has made it possible to convince judges to implement this law, and so this practice is currently expanding.

Unlike the situation in Vietnam, where an internationally financed, large-scale multiagency partnership produced a major "roll out" of methadone treatment and other addiction services, the situation in Lebanon was on a smaller scale, but the accomplishment was equally impressive. The introduction of buprenorphine and other outpatient evidence-based services was the result of the persistence and commitment of Lebanese clinicians, the Pompidou Group, UNODC, National Aids Program, and WHO, together with receptive Ministry of Health officials. The use of opiate substitution therapy in the Middle East is very limited, as public health pressure for introducing this treatment is limited due to the low rates of HIV throughout much of the region. The political situation over the past decade in Lebanon has made it challenging to bring the issue of addiction treatment onto the governmental agenda. However, the diligence of a small group of dedicated professionals, together with international organizations has added an important addiction service in Lebanon and has provided an example for the region of the feasibility and value of medication-assisted treatment for addiction.

75.2.1.3 Abu Dhabi, United Arab Emirates (UAE)

Abu Dhabi is one of the seven Emirates on the Persian Gulf that make up the United Arab Emirates, a country of great wealth as a result of its extensive petroleum production. The population of the UAE is approximately eight million. It is a country of rapid change and extensive infrastructure development in all areas, including health care. The National Rehabilitation Center (NRC) was established in 2002 under the direction of the late President of the UAE. It is the principal source of treatment and rehabilitation for Emiratis who have substance use disorders. It is also the organization that coordinates all aspects of drug abuse epidemiology, prevention, and workforce development. As of 2008, the NRC consisted of an 18-bed residential treatment and rehabilitation center, a nine-bed halfway house, and some outpatient services. The NRC was the officially recognized addiction treatment facility in Abu Dhabi, even though there were also some detoxification services provided in the major mental hospital in Abu Dhabi and some private psychiatric services were available.

In early 2009, a six-person team representing the International Society of Addiction Medicine was invited to visit the NRC to provide technical assistance and recommendations for service development. At the time of this site visit, the NRC had a patient census of nine patients who were undergoing extended hospital-based residential care for 9–12 months and three individuals living in the halfway house. At that point, the majority of the patients being treated in the NRC facility were individuals released from prison, and it was not altogether clear if the NRC was completely a clinical program or if it also served as an extension of the prison authority. The nature of treatment services at the time was somewhat unclear, and while there were some very well qualified and knowledgeable psychiatrists and clinical staff, there was minimal organization to the clinical program being offered and little indication of evidence-based practices being offered.

Over the next 3 years, the NRC instituted a major expansion of addiction services, with a commitment to developing a quality continuum of care based on

evidence-based medicine. The NRC recruited a medical director from Cairo University, Egypt, who was then the president of the International Society of Addiction Medicine, and two other Egyptian psychiatrists who had extensive expertise and specialized training in addiction. The NRC appointed a training director who, together with a training expert from Kings College in London, implemented a comprehensive program of staff training in evidence-based practices with quality clinical supervision. A team of clinicians received extensive training in the Matrix Model of outpatient treatment to address the substantial problem of ATS use and dependence, and the NRC arranged for the importation of Suboxone to treat opioid dependence. A research director, who had previously held a senior position at NIDA, was hired to develop a program of clinical and services research. In 2013, an electronic medical record (EMR) system was implemented, and, at present, the entire clinical record-keeping system at the NRC is incorporated into this EMR system.

The NRC has moved from the 18-bed residential facility in the city of Abu Dhabi to a much larger set of offices and villas in the suburbs of Abu Dhabi. The residential capacity has been expanded to 110 beds for men and a separate facility for women. Outpatient services (medical services, psychiatric services, addiction medications, and behavioral treatments) are integrated with the residential programs into a connected continuum of care. The treatment capacity has increased fivefold, from 67 patients treated in 2009 to 338 in 2012. Plans are underway for the development of a satellite facility in a northern sector of the Emirates to make services more geographically accessible, and ground has been broken for a comprehensive treatment center that will provide an even greater treatment capacity. The service development at the NRC over the past 5 years has been extensive, and a foundational part of the service philosophy is the use of good science and treatments with a strong evidence base.

75.3 Conclusion

The early twenty-first century has seen an expansion of addiction treatment services throughout the world, with evidence-based treatments applied as core features of the service continuum. This application of medical and behavioral health research findings to addiction service system development is a welcome step toward the establishment of drug treatment as a public health domain. As these services evolve and demonstrate effectiveness in reducing drug use and related infectious disease and drug-related crime, a significant challenge will be to find and mount the political will to redirect investments from incarceration/public safety interests to addiction treatment/public health interests that require preventative and clinical skills, medication, and coordination with related health conditions services.

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National Rehabilitation Center in 2009 and provided consultation to the NRC on outpatient services. Dr. Rawson and Dr. Rieckmann are Co-Principal Investigators on an evaluation of the Skoun Program in Beirut, under contract to the Drosos Foundation. Victor Capoccia was supported by UNODC to describe the development of community-based care in Vietnam in June and July 2012.

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Addiction Treatment in Iceland

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Abstract

This chapter aims to present various facets of addiction-related problems in Iceland and the unique features of Icelandic society that have molded the attitudes and ways of dealing with these problems. Although Iceland is geographically isolated, it has seen changes in drug use following international trends. Due to the small size of the population and its centralized health care, Iceland is in a unique position to follow such trends and monitor the course of those treated for addiction. These trends in drug use as well as epidemiological information and social policy issues are discussed. The development of addiction treatment services in Iceland is also reviewed with special emphasis on social aspects of treatment, such as high availability of treatment and the equality of access to health care. These aspects have yielded a smaller treatment gap in Iceland than in many other countries. In addition inpatient

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treatment services in follow-up care have been preserved within the addiction treatment system, complementing a comprehensive treatment model of addiction with a view of addiction as a chronic disease. These features are discussed in order to highlight their importance and contribution to effective clinical practices.

76.1 Introduction

Substance use disorder treatment in Iceland has a history spanning more than 50 years, during which treatment approaches and the general understanding of substance use disorder have changed dramatically. The development of treatments has been influenced both by general advancement in medicine and psychosocial treatments and by unique factors of the Icelandic society. This chapter reviews these cultural aspects of addiction-related attitudes and describes addiction treatment in Iceland with the aim of highlighting factors important in understanding how different societal factors may impact addiction treatment in an international context.

76.2 Treatment in Iceland

Iceland is a small island country in the North Atlantic Sea with a homogenous population of 321,857 (Statistics Iceland 2013). It is sparsely populated, with more than two-thirds of the population living in the capital of Reykjavik or its neighboring towns. Icelandic society upholds a Nordic social welfare system providing universal health care, including substance use treatment, and tertiary education for all. Equality is greatly valued and Iceland has been rated the country with the world's smallest gender gap 5 years in a row by the World Economic Forum (2013) reflecting equal access to education and health care. The standard of living is high and Iceland has been ranked as the 13th most-developed country in the world by the United Nations' Human Development Index (2013).

These unique features frame the substance disorder treatment system and high accessibility to treatment resulting in a smaller treatment gap than in most other countries. It has been estimated that in the United States, only one in ten in need of addiction treatment receives it (NDSUH 2010), compared to estimates of 50 % receiving treatment needed in Iceland (Tyrfingsson et al. 2010).

In addition to accessibility to services being high, another important aspect of the treatment milieu is that addiction has been seen as a biological disorder needing professional treatment. Treatment has thus been part of mainstream health care with treatment being provided by health-care professionals such as physicians, nurses, addiction counselors, psychologists alongside social workers, and other health-care professions. Thus, the emphasis has been on the disease model of addiction. This view of addiction among professionals is disseminated to the mainstream, making it easier for people to address their addiction problems, and this is reflected, e.g., in the lenient outlook of most employers who grant sick leave on pay for those

seeking addiction treatment. Social security also provides financial support to those with substance use disorders, just as for any other medical condition further reducing barriers to treatment.

Alcohol and drug policies have been strict in Iceland and have shaped consumption patterns. Alcohol sales are controlled and monopolized by the government, and the price of alcohol and tobacco has been kept high. Iceland has been second only to Norway for the highest retail prices of alcoholic beverages in Europe (WHO 2012). Strict tobacco use restrictions have led to steadily decreasing rates of smoking in the general population with the current rate standing at 17.4 % (Directorate of Health 2012); however, nicotine addiction has been relatively stable at 79 % among patients receiving addiction treatment (SAA 2012).

Drinking patterns in Iceland have been similar to drinking patterns in the Nordic countries. These patterns were characterized by infrequent use of alcohol, mainly heavy drinking or binge drinking of strong liquor, for the purpose of intoxication during weekends or festivities as the Scandinavian Drinking Survey in 1979 carried out in Iceland, Norway, Sweden, and Finland showed; in addition there was a higher level of acceptance of drunkenness in public than in other countries (Makela 1984, 1986; Room 2010; Room and Mäkelä 2000). The overall volume of alcohol consumption in the Nordic countries has been lower than the EU average, and Iceland has had the lowest consumption of alcohol per capita of the Scandinavian countries, with alcohol consumption rates of between 4 and 5 l from 1970 (3.82 l) until the 1990s, when consumption showed an increase when beer was legalized 1989, but its sale had been banned from 1915. The total amount of alcohol consumption has risen steadily since the introduction of beer, and sold liters of pure alcohol per capita, 15 years and older in 2012, were 6.93 l. In addition to increased alcohol consumption, there has also been a shift in consumption patterns from distilled spirits to beer (Olafsdottir 1998, 2002), and consumption of wine during the last decade of the twentieth century increased by 80 % (Directorate of Health 2003) with drinking patterns becoming more similar to those in Western Europe. However, Iceland still holds the distinction of having one of the lowest rates of alcohol consumed in Europe or almost half the mean rate of consumption in the EU countries (12.5 l pure alcohol per year) but higher than the global average of 6.1 l per capita consumption (WHO 2011).

Thus, strict alcohol legislation and a good treatment system have gone hand in hand in the effort to tackle the harmful consequences of alcohol abuse. Despite lower rates of consumption, the prevalence rates of substance use disorders have been similar in Iceland as in other countries. A recent study (Stefansson and Lindal 2009) of the prevalence of mental disorders in Reykjavik and its' vicinity using a random sample of three birth cohorts (born 1931, 1951, and 1971 and aged 34, 54, and 74 during the assessment) showed that the lifetime prevalence of the ICD-10 mental and behavioral disorders due to use of alcohol was 10.8 % with 1-year prevalence for alcohol use disorder 6 %, being more prevalent among men. These are similar to prevalence estimates using DSM-IV diagnoses in epidemiological surveys in the United States, showing prevalence of lifetime and 12-month alcohol dependence rates of 12.5 % and 3.8 % (Hasin et al. 2007).

Treatment of alcohol and drug use disorders in Iceland has involved different treatment settings with mental health services and specialized alcohol and drug services as the main providers of treatment for people with alcohol and drug use disorders. Services for this population began with the foundation of a rehabilitation home (Bláa bandið) based on AA principles in 1955, following the foundation of AA in Iceland 1954, with two meetings per week. Icelanders embraced the AA tradition from the start and today it is thriving, with about 300 meetings per week (see Olafsdottir 2000 for the history of AA in Iceland). Substance use disorder treatment has emphasized the AA approach and encouraged patients to engage in the AA community. The rehabilitation home was shortly subsumed into the mental health-care system.

The next significant development in addiction treatment in Iceland was during the 1970s. A number of people went to the United States for treatment and were exposed to what is called the Minnesota Model, consisting of intensive treatment for 4–6 weeks based on the 12-step approach of AA. Those that came back energized the AA society and decided to form a nonprofit layman's association for the advancement of alcohol treatment in Iceland. This association, Society of Alcoholism and other Addictions (SAA), was founded in 1977 and had as its goal to inform and influence the general public on the nature of the disease of alcoholism and to establish treatment and counseling services. Thus, the emphasis was placed on the disease concept, and the treatment of alcoholism was seen as a health-care issue as opposed to a social problem. SAA's treatment for addiction was started that same year, 1977. SAA built Vogur Hospital, the National Center of Addiction Medicine, in 1980 with donations from the Icelandic people to serve as a national center for addiction treatment. Vogur Hospital thus gained the recognition of the nation as the main addiction treatment facility, a welcome addition to the services provided by the National Hospital. The availability and salience of treatment options grew dramatically and high rates of available treatments have been maintained ever since (Olafsdottir and Helgason 1988). This high rate of available treatment is also unique to Iceland. The WHO has estimated worldwide that there are 1.7 beds per 100,000 population available for the treatment of drug and alcohol use disorders, with Iceland ranking the highest, with 52.4 beds according to the report on Resources for the Prevention and Treatment of Substance Use Disorders (WHO 2012).

Since its establishment SAA has become the leading treatment facility of alcohol and drug dependence in Iceland providing treatment at Vogur Hospital to more than 22000 patients (15.880 males (70.9%) and 6.522 females (29.1%)) or a significant proportion of the nation (10.5 % males over 15 years of age and 4.4 % of women of the same age). Approximately 1,800 individuals are admitted each year to Vogur Hospital, with about 600 newcomers annually with roughly 2,400 admissions yearly or 6–7 patients daily. This accounts for a large proportion of the treatment addiction services in Iceland. At the University Hospital Psychiatric Ward, about 500–600 patients are admitted yearly, mostly patients with concomitant mental (50 %) or other physical disorders (38 %) (Birgisdottir 2013). Other facilities that provide rehabilitation services are outside of mainstream health care.

76.2.1 Services at SAA's Facilities

Most patients start their treatment in detoxification at Vogur Hospital. They are mostly self-referred. During the average stay of 7–10 days, patients are detoxified, mental and physical diseases are stabilized, and psychoeducation is started and the process of motivation for change begins. Personnel consist of health-care professionals working full time, most are certified, as well as students in training. These include medical doctors, registered nurses and nurses' aids, and certified addiction counselors. In addition to Vogur Hospital with its 60 beds for adults and 11 beds for adolescents, SAA runs two inpatient rehabilitation centers, each with 30 beds with services tailored to specific groups (women, older men, younger men); three outpatient units, two in the capital Reykjavik and one in a town on the north coast, Akureyri; a recovery house with 20 beds for IV users without a home; and a social center.

After detoxification at Vogur Hospital, a majority of patients or two-thirds continue treatment and rehabilitation. One-third goes for further therapy in a residential setting (4 weeks) and one-third to intensive outpatient (4 weeks) after detoxification. Recognizing that better outcomes are related to adequate treatment length (NIDA 2009), residential treatment is the treatment of choice and treatment providers collaborate with the patient and aim for intense treatment options when possible and appropriate. Residential treatments are delivered in nonhospital settings outside of the city. Residential treatment consists of daily group therapy sessions and psychoeducation as well as individual counseling if needed (total of 60 h of treatment). Self-help meetings are facilitated in order to help patients gain community-level support to support recovery and maintain abstinence after formal treatment ends, with an additional 3 months of weekly sessions (additional 12 h treatment). The follow-up phase of the inpatient option consists of biweekly sessions for 3 months (24 h total) followed by weekly sessions for up to 9 months (36 h total). Group therapy and individual counseling sessions are guided by principles and techniques of cognitive behavioral therapy and motivational interviewing and are delivered by certified addiction counselors. Treatment protocols and staff training follow the NIDA recommendations (2012) of an evidence-based approach to treatment and training. Recognizing that addiction is a chronic disease, readmissions are not uncommon and are welcomed. About half of the patients that have come for treatment over the past three decades have been admitted only once to the hospital, and the majority, 78 %, three or fewer times. A subgroup of patients need additional assistance and about 4 % have been admitted more than 10 times.

Another important aspect emphasized in SAA treatment services is relapse prevention, and follow-up treatment is provided for up to 1 year as described above, with less intense outpatient services following the more intense options to closely monitor progress and support relapse prevention.

SAA offers a wide range of treatment options tailored to various levels of disease severity and different needs of patients based on factors such as gender and age. These specialized treatment options range from opioid maintenance therapy to adolescent

treatment; in addition there is specialized treatment for women, for men over 55 years of age, and for relapse-prone men; treatment is offered for gambling and to families dealing with addiction. Treatment modality also varies, with counseling, education, and group therapy provided within both inpatient and outpatient rehabilitation settings, with long-term treatment available for the most severely affected patients and an intensive outpatient therapy with assisted housing. Particular emphasis during the last decade has been placed on counseling one of the high-risk groups in a preventive effort, i.e., the children of patients growing up with the addiction.

76.2.1.1 Changes in Addiction-Related Problems

Because SAA has been a lynchpin in addiction treatment delivering a high proportion of treatment to all Icelanders, the treatment cohort is representative of the Icelandic treatment-seeking population. Clinical data have been gathered in a systematic way over the past two decades providing DSM-IIIR/DSM-IV diagnoses as well as other clinical information. This unique database provides important information and allows for tracking trends in the patient population. To name a few, the makeup of the patient population has changed with the proportion of women increasing over the years (about 20 % of hospital admissions in 1980s, increasing steadily to 30 % of admissions during the past decade), as well as patients being admitted at a younger age than before. Another age trend has been an increase in admissions of patients over 55 years of age, possibly reflecting changes in drinking habits within this age cohort (less binge drinking and more daily drinking over a period of years). The majority of patients are treated for alcohol dependence, but the proportion of these patients has given way to other substances over the years. In 2012, 41 % of patients had a primary diagnosis of only alcohol use disorder alone, while more than half of the patients were also diagnosed with other substance use disorders in addition to alcohol mainly cannabis (21 %) and amphetamine (13 %). Iceland has never had a problem with heroin; however, opioids are abused, with about 4 % of the patient population seeking treatment for opioid dependence. About 80 patients currently receive opioid maintenance therapy, mostly with buprenorphine but some with methadone.

There have also been changes in substances of abuse. The abuse of amphetamine has been a growing problem in Iceland while the use of cocaine has subsided mainly because of its' high price. Over the past decade, the number of patients seeking treatment for amphetamine dependence has almost tripled, and in 2012, 39 % of all of patients seeking treatment at SAA had a diagnosis of amphetamine dependence (SAA 2010). In addition to the marked increase in amphetamine addiction, amphetamines are also being used intravenously (IV), thus markedly increasing the risk for hepatitis and HIV. SAA is seeing most of the injectors as it is estimated that 90 % of IV users have sought treatment at SAA. The prevalence of hepatitis C was studied among IV amphetamine users that entered treatment at SAA between 1991 and 2006, and it was found that approximately 30 % were infected. Infections were related to the frequency of injection; 14 % of patients that injected amphetamines less than ten times in the previous year were infected, while among those who injected regularly, 60 % were infected. Outside this population of amphetamine injectors, hepatitis C

infections are rare in Iceland as is HIV, though the situation could change rapidly if injecting use continues and spreads. Currently the abuse of methylphenidate, mainly provided by medical subscription, has rapidly risen the past years, and Iceland is second only to the United States in the medical consumption per capita of methylphenidate from 2004 to 2009 (Kaye and Drake 2012). Other IV substances used in Iceland are also prescription drugs, mainly opioids.

The use of amphetamines by adolescents is another area of great concern as use in this age group has steadily grown over the past 15 years. For example, among those 19 years old and younger and seeking treatment at SAA, over 92 % have tried amphetamines and over 60 % reported using amphetamines weekly for six or more months (SAA 2010). Previously, regular users in this age group entering treatment at SAA were few (less than 30 per year before 1995) but the numbers recently doubled, and sometimes tripled, with admissions ranging between 100 and 150 regular teenaged users annually, mostly 18 or 19 years of age.

Looking at all diagnoses, primary and otherwise, the proportion with cannabis addiction has doubled over the past 20 years, and now about 35 % of the overall patient population in treatment meet diagnostic criteria for cannabis dependence. Among those younger than 25 years, cannabis is the main substance of abuse although multiple drug use is most common. Two-thirds (76 %) of young people 19 years old and younger meet criteria for cannabis dependence and 62 % meet criteria for amphetamine dependence (SAA 2010). Thus, international trends are reflected in the patient population.

76.2.2 Treatment Outcomes

Studies on treatment outcomes have been scant in Iceland. In an Icelandic study on the genetics of addiction (Tyrfingsson et al. 2010), survey data collected on abstinence rates of 920 patients previously seeking treatment at SAA showed that 59 % had been abstinent for the past year and 51 % had been abstinent the past 2 years. Twenty-seven percent reported having used alcohol or other drugs during the past month. This gives an indication of treatment success in regard to abstinence rates. These rates of remission of disease are quite good considering the chronic nature of the disease. This is an area in need of further research.

Another way of evaluating treatment outcomes is assessing dropout rates. At Vogur Hospital, the first point of entry of treatment at SAA, about 20 % of all admissions do not finish the recommended length of stay (average 10 days), but 70 % complete detoxification and are discharged with a plan for further treatment, which is regarded a successful completion of the stay.

76.3 Conclusion

In summary, addiction treatment at SAA provides a comprehensive treatment approach for a medical disease of the brain, a variety of options at different levels

of care. It offers medically assisted detoxification and a well-structured psychosocial treatment approach. The motivation and intent of the patient is reevaluated repeatedly and treatment planning negotiated according to changing patient's needs. It emphasizes a continuum of care akin to the treatment of other chronic diseases, where relapses are seen as a need for increased treatment. The access to treatment is exceptional, as no specific referral is needed and admission is free of charge. Treatment is tailored to meet the needs of specific groups, such as adolescents, women, older, relapse prone, opioid dependent, and pregnant women are admitted to services without delay. Close collaboration is maintained with specialty care, such as psychiatric, infectious disease, emergency room, and social services. Screening for blood-borne infections is thorough, other medical and mental disorders are treated as needed, and referral to special care is followed through. Twelve-step self-help groups are introduced and encouraged.

This treatment approach is based on the disease model of addiction, and SAA has emphasized disseminating this view of addiction in order to reduce stigma and decrease treatment barriers. This has been a key element in decreasing the treatment gap, along with other social system variables such as equality in access to health care and socialized medicine for all. Strict alcohol and drug policies have simultaneously been enforced thus supporting prevention efforts. The AA community in Iceland has been a strong force and is a key factor in supporting recovery in patients. In order to continue improving treatment of addiction, we must address issues of dropout and preserve long-term treatment options under pressures of delivering treatment in an outpatient setting only in the brief term. It is clear that staying in treatment is the most important aspect of any therapy, and at SAA the inpatient settings are conducive to adherence to treatment and are thus vital to ensure good treatment outcomes.

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Section VI

Main Elements of a Systems Approach to Addiction Treatment

Ambros Uchtenhagen and Giuseppe Carrà

Main Elements of a Systems Approach to Addiction Treatment: An Introduction

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Ambros Uchtenhagen and Giuseppe Carrà

Abstract

This section is dedicated to a range of issues which go beyond the clinical practice in providing specific treatment options to specific populations, in specific services by specialists or in primary health care. The focus here is on the treatment system in the community, at a regional or national level, as a comprehensive network integrating different approaches, services and actors, including harm reduction interventions. The various aspects of building up such a network and of improving an existing system are discussed, legal and ethical frameworks and rules are described, as well as the evidence base for good quality interventions and ways how to monitor and evaluate their outcomes.

The focus on the treatment system as a comprehensive network of all services, covering all types of addictive behaviors. implies the preference for a public health perspective, combining the care for the individual patients in their diversity with the intention to cover the treatment needs in a specific catchment area and for a given population.

This aim has to consider the availability, affordability, and accessibility of appropriate and qualified treatment. It has to build on effective treatment, provided in an efficient and cost-effective way. It has to stress connections among services, shared concepts of different indications, and routine rules for patient pathways through treatment phases, ranging from first contact, screening, and assessment to treatment planning and monitoring, rehabilitation, and aftercare. Pathways may

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also follow models of stepped care in an attempt to avoid misplacement of patients and to make best use of the available human and financial resources.

A comprehensive network goes beyond formal therapeutic regimes, by including low-threshold approaches for establishing contact by outreach activities, by harm reduction interventions in support of those still actively engaging in addictive behavior. This includes measures to reduce the risks of injecting, of acquiring blood-borne infectious diseases, and of overdose-related mortality. Such interventions are not in contradiction to others offering a structured regime of substitution medication (e.g., for opiates or nicotine) or even aiming at abstinence from substance use and full recovery. The system has to integrate all these approaches in order to best meet the needs and preferences of the equally diverse people with substance use disorders. Everyone should be able to find what is appropriate and suits him or her best under present conditions.

Such a comprehensive network is work in progress, as addictive behaviors and treatment populations change over time. New therapeutic methods and instruments also ask for adaptation and suited implementation at the system level. Where no such network is in place, the relevant steps for building up a system responding to the needs are recommended. All this goes not without a political support to provide adequate and sustainable resources, in the framework of a treatment policy which is in line with an overall drug policy.

Major instruments for assessing process and efficacy of the treatment system are monitoring and evaluation. They allow the identification of weaknesses of the system, as a starting point for improvements. Monitoring and evaluation are crucial for adapting the system to new challenges. A certain flexibility and readiness for adaptations are pivotal for their implementation. Education and training of staff, including continued education, are instrumental not only for good quality and best practice but also for such implementation.

Quality of intervention is embedded in evidence base, also in the field of drug addiction treatment. It is crucial that all the stakeholders, including drugs users, their families, and the public, are involved in the selection of priorities to offer the best possible evidence-based treatment. Language to translate evidence thus needs to be understandable to empower stakeholders.

A solid basis of the treatment system must include the consideration of ethical and legal aspects. Human rights and medical ethics apply. National legislation and international conventions are to be respected or – if outdated or ineffective – revised. The prominence of designing treatment systems creates opportunities, challenges, and dangers for addiction scientific community. The future standing of the specialty will depend on not only the practical utility of its responses to those opportunities and challenges but also the ethical integrity of those responses.

Treatment Systems for Population Management of Substance Use Disorders: Requirements and Priorities from a Public Health Perspective

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Thomas F. Babor

Contents

Abstract

This chapter describes the requirements and priorities of service systems designed to treat persons with substance use disorders. Research and theory are reviewed to inform policymakers, program administrators, and treatment providers about the best ways to organize or to expand treatment services using a public health systems perspective, which is concerned primarily with how services contribute to the health and welfare of a population. The requirements of a service system include sound policies (especially stable financing); appropriate structural features, such as facilities and trained personnel; and services that are accessible, affordable, and integrated. The priorities for establishing such a system will depend on the assessment of population needs, as well as needs-based planning and the support of mutual help organizations. It is concluded that a public health approach to the development of treatment systems provides a useful way of responding to the changing needs of the population in relation to substance use disorders.

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78.1 Introduction

At a time when health-care delivery is changing rapidly throughout the world and new substance abuse treatment services are being developed and evaluated, it is critical that services for persons with alcohol and drug problems be delivered in the most effective as well as in the most efficient manner. The focus on treatment system issues represented in the title of this chapter is designed to direct attention at the growing body of research and theory that can be used to inform treatment planning and quality improvement at the community and national levels.

The development of an effective treatment system is a crucial part of a country's public health response to the problems associated with substance use disorders. Although a great amount of research has been conducted on treatment of substance use disorders, most of it deals with clinical issues, such as the efficacy of different psychotherapies or pharmacotherapies, rather than the larger treatment policy issues that often result from tradition, budget constraints, or political decisions. As described in a conceptual paper by Babor et al. (2008), what is now needed is a comparable effort to use systems-level research to inform policymakers and program administrators about the best ways to configure or to expand their treatment services in order to maximize the impact of treatment services at the population level.

This chapter deals with the requirements and priorities of the treatment system, which are approached from a public health perspective. The requirements of a service system include sound policies (especially stable financing); appropriate structural features, such as facilities and trained personnel; and services that are accessible, affordable, and integrated. The priorities of such a system include the accurate estimation of population needs through service mapping and needs assessment, as well as rational service planning that includes an emphasis on community support networks such as mutual help organizations.

78.2 Concepts, Requirements, Priorities

78.2.1 Definitions and Rationale

A treatment system for persons with substance use disorders is an arrangement of facilities, programs, and personnel that is designed to function in a coordinated way. Such an arrangement includes linkages between specialized care and other types of services, such as mental health, general medicine, social welfare, criminal justice, and mutual help organizations (Babor et al. 2008).

The focus on the arrangement and coordination of services, rather than just the personnel, programs, and therapeutic aspects of treatment, raises a new set of questions for clinicians, program administrators, and policymakers. Can systems concepts help to reduce the gap between population needs and the current availability of substance abuse services? How can treatment services be made more accessible to those in need? Are the needs of affected populations being met by the

current array of services? Are services being distributed and accessed appropriately? Are screening and referral conducted at gateway institutions, such as primary health care, schools, and employment settings? Are there appropriate diagnostic capabilities? What are the most effective administrative linkages between substance abuse services and criminal justice, mental health, general medicine, primary care, and other human services? Are they coordinated with other specialized services in a continuum of care? Are evidence-based services available and relevant? What is the policy support for integrated structures? What can be done to build stronger community support networks (e.g., AA, family social clubs)? To what extent can mental health and general medical services be better integrated with addiction treatment? Are there advantages to having separate systems for substance abuse, or should they be integrated administratively with services for other health conditions or social problems?

These questions define issues that can be addressed by a public health systems perspective, which is concerned primarily with how services contribute to the health and welfare of a population. Services for substance use disorders expanded dramatically in developed countries in the 1970s but often in a fragmented and arbitrary way. Resource allocation decisions and treatment policies have a major effect on the development of services for persons with substance use disorders, but there is little knowledge to guide service planning or to indicate whether services achieve their public health objectives. Low- and middle-income countries are now investing in services as substance use prevalence rates increase with rising incomes, but there is little systematic knowledge to guide the development of service systems that would best address the needs of their populations.

78.2.2 History and Conceptual Developments

Conceptual, theoretical, and empirical work on treatment systems is a recent development, but substance abuse treatment has a long history that can be traced back at least 200 years in some countries (White 1998; Souria 1990). A rudimentary set of treatment services, mostly specialized residential programs, emerged from the nineteenth century asylum movement originally designed for mental patients but which also served large numbers of alcoholics (White 1998). Since the 1960s in the industrialized countries, there has been a steady growth of specialized medical, psychiatric, and social services for individuals with substance use disorders (Makela et al. 1981). Although each country developed a different mix of services and administrative structures, there were some commonalities across national systems in the types of service settings (residential, detoxification, and outpatient) and therapeutic approaches (Klingemann and Hunt 1998). As treatment services became more numerous and specialized, new concepts were developed to describe how they related to the different types of population needs. These concepts include the continuum of care, broadening the base of treatment, the chronic care model, and service system levels.

The *continuum of care* concept, as described by Rush et al. (2013), refers to the mix of services available to patients and the way patients are expected to pass through it. The services are generally arranged sequentially beginning with screening and diagnostic assessment and then assignment to different settings and services depending on acuity, severity, and complexity. The main services that have been incorporated into the systems framework in most countries are withdrawal management and detoxification, residential rehabilitation, outpatient counseling, continuing care, and community support networks such as Alcoholics Anonymous. Variations of the continuum of care concept are the core-shell model and the stepped-care approach. In the core-shell model, core functions, such as intake assessment and treatment assignment to the most appropriate type of care (the shell), are facilitated by case management (Glaser et al. 1978). In the stepped-care approach, patients are assigned to the least intensive level of care initially. If outcomes are not optimal, they can be "stepped up" to a more intensive level, and if outcomes are positive, they can be "stepped down" to appropriate continuing services.

Another innovation that has contributed to the systems concept is SBIRT, which refers to screening, brief intervention, and referral to treatment, typically in the context of early intervention in primary health-care settings (Babor et al. 2007). The SBIRT model grew out of a seminal report issued by the US Institute of Medicine (1990), called *Broadening the Base of Treatment for Alcohol Problems*. SBIRT is a comprehensive and integrated approach to the delivery of early intervention and treatment services through universal screening for persons with substance use disorders and those at risk. Beginning in the 1980s, concerted efforts were made by the World Health Organization (WHO) to provide an evidence base for alcohol screening and brief intervention in primary health-care settings, in order to *broaden the base of treatment* in countries where specialized services were unavailable. With the development of reliable and accurate screening tests for alcohol, more than a hundred clinical trials were conducted to evaluate the efficacy and cost-effectiveness of alcohol screening and brief intervention in primary care, emergency departments, and trauma centers (Babor et al. 2007).

Just as SBIRT attempts to integrate specialized substance abuse treatment services with outreach to the general health-care system, the *chronic care model* addresses the needs of more serious cases of substance dependence by coordinating specialized services over time under the assumption that once substance dependence has developed, there is a need for continuing care and management, as is done with chronic conditions like diabetes and hypertension. The chronic care model has been adapted to substance abuse by Rush (2010, 2013) who has defined a series of "tiers" that constitute the most important elements of a continuum of services for the management of chronic substance users. Five tiers are defined on the basis of their functions, which are higher-order groupings of similar services or interventions.

Tier 1 refers to health promotion and prevention functions targeted at the general population. This tier recognizes the likelihood that public policies, the regulatory environment, and lifestyle factors contribute to the risk of substance abuse and the

need for treatment. Tier 2 consists of early intervention and self-management functions directed at persons at risk. This incorporates the SBIRT activities that have provided an important link to other health-care settings. Tier 3 consists of treatment planning, crisis management, and support functions for persons with identified substance-related problems. Tier 4 includes specialized care for people in need of more intensive services, such as residential programs, outpatient counseling, and pharmacotherapy. Finally, Tier 5 comprises highly specialized care functions for individuals with complex problems, such as inpatient withdrawal management, forensic services, or long-term psychiatric care. The tiered framework is designed to be used as a planning tool for the development of an integrated system of service functions for substance abuse, mental disorders, and gambling problems.

Despite the growth of treatment services and systems of care in many countries, the services in most parts of the world are fragmentary and lack coordination. Four development levels have been proposed to account for the range of systems that have evolved in different countries (Babor and Poznyak 2010). Level I refers to services that are "minimal" in relation to population needs. If they exist at all, services tend to be fragmentary, with rudimentary care available in some settings (e.g., emergency departments or psychiatric wards) and perhaps specialized services in medical and psychiatric settings where a residential unit might provide training and care for a limited number of patients. Level II is described as "limited" in terms of systems development, with some specialized services in medical and psychiatric settings. Level III refers to a "modest" level of development where a variety of services are delivered in most settings and there is some regional coordination and planning. Level IV refers to "mature" systems, with a variety of integrated services in a range of settings and stable financing for these services. The specification of these levels is useful for suggesting ways in which a system at a particular level of development can be improved and for monitoring changes in systems development over time.

78.2.3 Requirements of an Optimal Treatment System

Babor et al. (2008, 2010) have described the components and dynamics of an optimal treatment system from a public health perspective. These are what have been referred to as the basic "building blocks" of a service system (Huntington et al. 2012). As described in Fig. 78.1, the first requirement is a set of policies that make the governance of the service system and its constituent parts possible. The second component is the system's structural resources, including infrastructure, technologies, personnel, programs, and facilities. The third component consists of system qualities, such as accessibility, economy, and efficiency, which contribute to the smooth functioning of the service system. According to this model, the policies, resources, and qualities of the system should not only translate into the effectiveness of services on individuals exposed to them, it should also contribute to population health through reductions in death, disease, and disability.

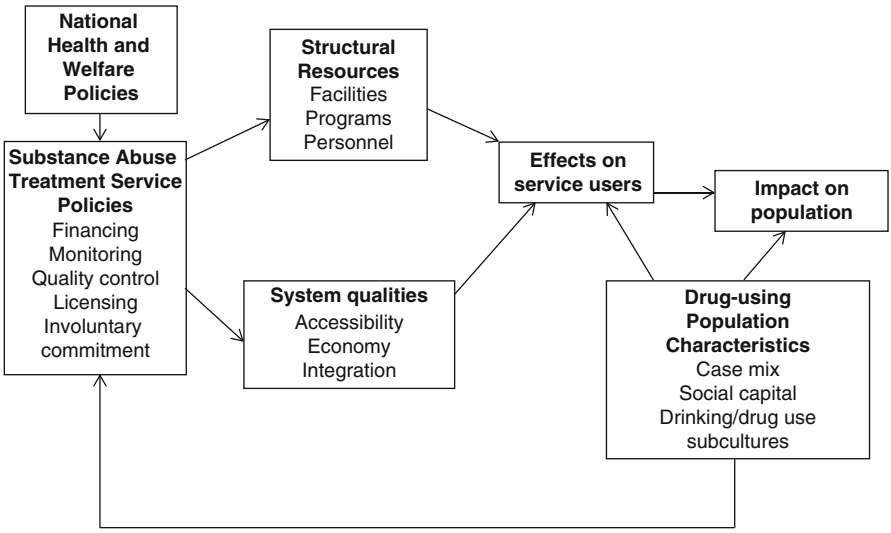

Fig. 78.1 Conceptual model of service system policies, resources, and qualities and their potential impact on population health (SOURCE: Adapted from Babor et al. (2008))

The components of this model and the research supporting it are discussed in the remainder of this section in order to indicate how a systems model might best contribute to population health.

78.2.3.1 Policies

The first requirement of an effective treatment system is appropriate treatment policies that provide a statutory basis for designing treatment programs, licensing treatment providers, and providing funding for programs and personnel. Policies determine the size, the administrative location, and the organization of the treatment system. They provide a framework for the allocation of resources.

According to Room (2010), there is a great deal of legislation for the treatment and rehabilitation of persons with substance use disorders, but much of the legislation is concerned with provisions for compulsory treatment or for treatment in lieu of jail. Other kinds of policy include national standards for clinical practices and licensing requirements for treatment personnel.

According to a survey conducted by the World Health Organization (2010), 66.2 % of the 145 countries surveyed have a government unit or government official responsible for treatment services for substance use disorders, but fewer than half of these countries have a specific budget line for these services. Financing mechanisms vary but most countries use tax revenues, user fees, and private insurance to pay for alcohol and drug services.

Resource allocation decisions have had a major effect on the development of these services. For example, the number and variety of services increased dramatically in the United States when the US Public Health Service invested in treatment

services as part of a broader public health approach to reduce the burden of disease, disability, and social problems that accompany substance use (White 1998). The rapid development of federally supported residential and outpatient treatment programs, along with an expansion of insurance coverage for private programs, established the feasibility of serving large numbers of alcohol- and drug-dependent patients within a specialized set of services.

Treatment policies and financing mechanisms affect the degree of centralized management of treatment services and their incorporation into other human service areas, such as social welfare, mental health, general medicine, and criminal justice. In Denmark, policies were used to decentralize treatment services, whereas in Norway, they moved the system toward a more centralized, medically oriented structure (Stenius et al. 2010). In Canada and the Netherlands, mental health and substance abuse treatment systems have been integrated (Rush 2010). In Finland, services are being reformed by merging mental health and addiction outpatient services and by emphasizing the management of patients in primary care (Kuussaari and Partanen 2010). Although policy changes designed to reform the organization of treatment services may have sound assumptions and a good rationale, they are rarely accompanied by systematic evaluation research to inform future decisions.

78.2.3.2 Structural Resources

The next requirement of an effective treatment system is to have sufficient resources to meet population needs and demands for treatment services. The core structural elements are facilities, personnel, and programs. Alcohol and drug services in "mature" treatment systems form a continuum ranging from primary prevention activities designed to ensure that a disorder or problem will not occur, through secondary prevention activities (including early identification and management of substance use disorders), to tertiary prevention activities that aim to stop or retard the progress of a disorder. In many countries, these services have generally developed separately and are rarely integrated into a single service delivery system.

Figure 78.2 summarizes data from the WHO *ATLAS on Substance Abuse* (2010) describing the most common settings in countries for the treatment of alcohol and drug disorders. In the plurality of the responding countries (39.8 %), mental health services are the most common treatment setting for alcohol use disorders, whereas the main setting for the treatment of drug use disorders (51.5 %) is specialized treatment services. Approximately 10 % of the countries reported primary health care to be the most commonly used setting for treating alcohol and drug use disorders.

Another structural resource is the capacity of the system in terms of the number of beds and length of stay. The median number of beds for alcohol and drug use disorders globally was 1.7 per 100,000 population (range 0–52) (WHO 2010). The lowest number of beds was reported in the African regions, whereas the highest number was reported from countries in the European Region (10.3 beds per 100,000 population). Median length of stay for drug and alcohol detoxification was found to be 14.0 and 10.3 days, respectively, with low-income countries reporting a longer median length of stay than high-income countries.

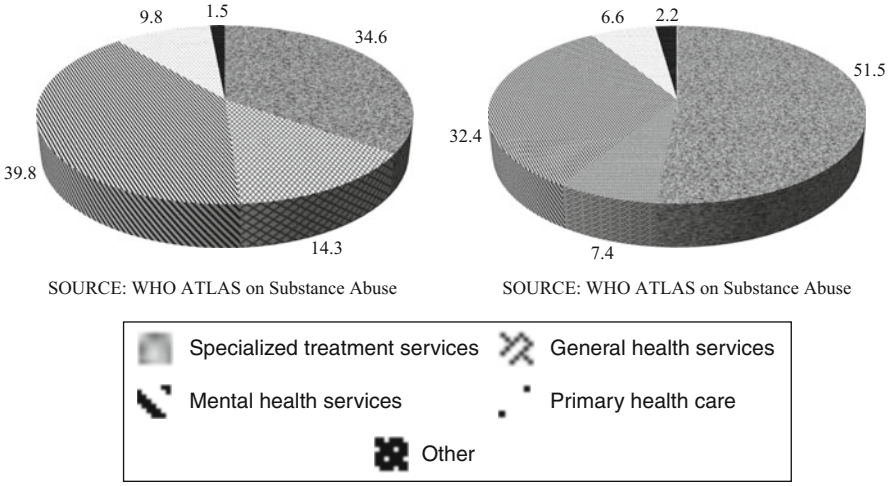

Fig. 78.2 Most common settings for treatment of alcohol and drug disorders in WHO member states

Finally, treatment personnel have become a central feature of a country's treatment infrastructure. Among the various health professions involved in treating substance use disorders, the majority of countries reporting in the WHO ATLAS include psychiatrists, general practitioners, and addictionologists/narcologists as the most important (WHO 2010). In addition to these professional addiction specialist groups, nonprofessional organizations have increasingly emerged as a critical part of the workforce in the formation of self-help organizations. Former alcoholics and drug addicts play an important role in providing community support services in many countries (WHO 2010).

78.2.3.3 System Qualities

Over time, the collection of services used to manage persons with substance use disorders takes on the characteristics of a system, with differences emerging not only in terms of policies and structural resources but also in terms of system qualities that characterize the functioning of a system. According to the model in Fig. 78.1, these qualities can be described in terms of equity, efficiency, and integration.

Equity refers to the extent to which services are equally available and accessible to all population groups. In South Africa, a study found inequitable access to substance abuse treatment services among the poor, with non-need factors, such as gender, mainly determining utilization (Myers et al. 2011). Access to treatment may be as important as the type of treatment. Findings from large-scale treatment matching studies indicate that the decision to enter treatment is associated with considerable reductions in drinking, but once someone is admitted to a particular program or is exposed to a particular type of psychotherapy, they do equally well regardless of their personal characteristics or severity of dependence

(Babor and Del Boca 2003). Thus, the value of different types of treatment may be to convince clients that treatment is going to help them. Research (Cooney et al. 2003) suggests that the key ingredient of the success of any therapy may be its ability to attract clients and generate enthusiasm among therapists. Instead of distinct nonoverlapping elements, therapy may work through common mechanisms, such as empathy, an effective therapist-client alliance, a desire to change, inner resources, a supportive social network, and the provision of a culturally appropriate solution to a socially defined problem. Thus, the more that treatment services are made available to all population segments, the greater the system's effectiveness is likely to be, regardless of the specific type of services.

Some therapeutic interventions are more cost-effective than others, suggesting that resources could be allocated more efficiently and economically without compromising effectiveness. One way to improve the efficiency of treatment is to organize treatment teams or sites to work together for a 12- to 24-month period with the aim of improving a specific area of care. This "improvement collaborative" approach combines traditional quality improvement methods of teamwork, process analysis, adoption of standards, training, and coaching. In a study by Gustafson and colleagues (2013), the use of collaborative methods, especially coaching, was found to decrease waiting time, improve treatment retention, and increase recruitment of new patients. Humphreys and McLellan (2011) found that process improvements can change the efficiency of treatment programs, but the link to better outcomes is weak, in part because outcomes are mainly influenced by environmental factors and life events outside of formal treatment.

System integration means the amount of interconnectedness among the organizations in a network. Research suggests several ways to improve system integration: drug courts, SBIRT, integrated treatment programs for pregnant drug users, managed care, and case management. There is some evidence to suggest that drug courts can increase social controls, lengthen the duration of treatment, reduce criminal behavior, and lower rates of recidivism (Eibner et al. 2006).

The elements of SBIRT have been evaluated in clinical trials and found to be effective (Babor et al. 2007) to such an extent that demonstration programs have been conducted in large population areas of several countries, including Finland (Seppä and Kuokkanen 2008), Norway (Aasland and Johannesen 2008), Denmark (Barfod 2008), South Africa (Seale and Monteiro 2008), Brazil (Souza-Formigoni et al. 2008), and the United States (Madras et al. 2009). Despite some successes in primary health care (Souza-Formigoni et al. 2008), the results of programs relying on the training of physicians and other health personnel without adequate logistical support have not been encouraging.

In the United States, a large-scale demonstration of programs operating in 27 states since 2005 has been found (McRee et al. in press) to enhance the states' continuum of care to include universal, adult SBIRT services in primary care and other community settings (e.g., health centers, nursing homes, university health centers, hospitals, emergency departments, and military). In an evaluation of SBIRT's system effects, McRee et al. (in press) found that the program filled

gaps in services for substance users in both the medical and specialty treatment systems of care. It was also associated with improved system equity (i.e., equal access to all population groups) and efficiency by extending services to underserved populations, expanding services within facilities and across tasks, and improving system linkages.

Another way to improve the integration of treatment is through integrated treatment programs. Examples include treatment of pregnant women who have substance use disorders and the delivery of mental health services to patients with co-occurring mental disorders. Integrated women's programs providing pregnancy and parenting services have been associated with improvements in child development (Niccols et al. 2012). But the results of integrating care for clients with co-occurring mental health and substance use disorders have been equivocal (Donald et al. 2005).

78.2.3.4 Effectiveness and Population Impact

When the requirements for an optimal treatment system are approached, treatment services are available, affordable, and accessible. Under these conditions, the system should not only deliver effective services, it should also have a population impact.

Effectiveness means the extent to which one or more services are responsible for positive changes in substance use and substance-related problems. Effective services should promote abstinence (or at least reduce substance use), prevent relapse, and address such substance-related problems as unemployment and marital adjustment. As suggested in Fig. 78.1, the impact of these services should translate into population health benefits, such as reduced mortality and alcohol-related disease rates, as well as benefits to social welfare, such as reduced unemployment, disability, crime, suicide, and health-care costs.

Can the integrative effects of prevention, early intervention, and treatment systems reduce population rates of alcohol and drug problems? This issue has not been investigated extensively, but there is suggestive evidence for such an effect. For example, growth in the availability of opioid maintenance treatment is associated with reductions in illicit opiate use, crime, and HIV risk behaviors in the United Kingdom, France, Norway, and the United States (Bukten et al. 2012; Marsch 1998). Increases in the proportion of alcoholics in treatment have been linked to decreases in liver cirrhosis morbidity (Mann et al. 1988; Holder and Parker 1992), and increases in AA membership and amount of treatment linked to decreased alcohol problems (Smart and Mann 2000).

Given the possibility that policies, resources, and system qualities, as core requirements, can be used to provide a more effective set of services and contribute to the system's public health impact, the next section of this chapter considers the main priorities for developing such a system.

78.2.4 Priorities

Substance use services have traditionally been established without the benefit of a comprehensive, quantitative planning process that is closely aligned with

population needs. Priorities for developing an optimal treatment service system will vary according to a country's current level of services, as well as the nature of their alcohol and drug problems. Among the highest priorities are service mapping, needs assessment, and service planning. Another priority that is often neglected despite its recognized effectiveness is the establishment and support of mutual help organizations that provide a critical community resource for the maintenance of recovery.

78.2.4.1 Service Mapping

Treatment service mapping involves the description of system structures and qualities. Treatment mapping research has been conducted in Hungary, Poland, the Russian Federation, France, Switzerland, Germany, the United Kingdom of Great Britain and Northern Ireland, the United States of America, Finland, Sweden, and a variety of other countries (Klingemann et al. 1992, 1993; Klingemann and Hunt 1998). Data collection tools have been developed for treatment mapping purposes, but most of these instruments do not examine the broad treatment system issues described in this chapter.

To promote the orderly planning and dissemination of evidence-based addiction treatment within national health-care systems, the WHO has designed a new procedure for assessing, monitoring, and evaluating treatment systems for substance use disorders, in relation to population needs (Babor and Poznyak 2010). The WHO Substance Abuse Instrument for Mapping Services (WHO-SAIMS) was developed to provide information on prevention and treatment services that can be used for policy planning, service design, and service improvement. In its present form, the WHO-SAIMS has a primarily descriptive function that identifies gaps in service delivery and areas for system improvement.

The primary purpose of the WHO-SAIMS is to examine the structure and functioning of alcohol and drug service systems in terms of resources, facilities, personnel, and programs. It can also be used at the national and subnational levels for monitoring and process evaluation to identify changes in the system over time and to assess the extent to which system improvement strategies have been implemented. In assessing how well the system functions, indicators include equity, efficiency, and accessibility, as well as system malfunctions such as waiting times for services, underutilization of services, and gatekeepers to access. The instrument asks detailed questions about the provision of alcohol and drug services in multiple settings, including specialist inpatient facilities, outpatient settings, and community programs. It also inquires about the professional sector's linkages with mutual help organizations and other lay service providers. It examines interactions between different levels of care, such as patient movements from less intensive to more intensive levels of care.

The WHO-SAIMS consists of a core instrument appropriate for use in all countries, irrespective of development level. The scope and configuration of the instrument are described in Table 78.1. The SAIMS also has supplementary modules that can be used for estimating the potential demand for treatment and

Table 78.1 Scope and configuration of the World Health Organization's Substance Abuse Instrument for Mapping Services (WHO-SAIMS)

Policy and legislative domain: includes items about national alcohol and drug policies; legislation governing drug control, prevention, and treatment; strategic plans that address substance use disorders, workforce development for substance abuse professionals, and resource allocation to and the financing of alcohol and drug services
The substance abuse situation and current alcohol and drug service needs: this section is designed to (i) help identify whether current services match needs and (ii) estimate service coverage
Current alcohol and drug treatment system. This domain describes the type and mix of services provided, service integration, and system complexity
The alcohol and drug services domain. This section covers (1) other residential services for alcohol and drug problems such as halfway houses and sober living environments; (2) alcohol and drug services provided by other sectors such as mental health facilities, primary health-care services, and the criminal justice sector; (3) the linkages between these services; (4) the availability of psychosocial treatments and psychotropic medications; and (5) drug substitution therapies and harm reduction services for opioid users
The primary care domain. Items in this category refer to interventions used in primary care settings
The human resource domain. This describes the quantity of human resources as well as human resource development, including mutual help organizations and recovering communities such as AA and NA

Source: Babor and Poznyak (2010)

treatment needs. (The WHO-SAIMS instrument and accompanying modules are currently being published for public use and will be made available on the WHO website.)

78.2.4.2 Estimating Treatment Needs and Demand for Treatment

Demand for treatment refers to the number of people who want to access treatment, including those who receive treatment (met demand) and those who want treatment but cannot access it (unmet demand). Unmet demand may exist because services do not exist, are not available, are too expensive, or are inaccessible.

Need for treatment refers to the number of people in a geographic region who meet the criteria for dependence or harmful use and who would benefit from treatment but do not access it. Some of these people want treatment but cannot access it (for the above reasons), while others do not want treatment nor do they seek it. The numbers of "unmet need" are likely to be greater than the numbers of "demand for treatment" as "unmet need" includes those people who do not perceive the need for or do not desire any treatment.

There are several methods to identify unmet treatment need, some involving primary data collection and others relying on secondary analysis of existing data sources. Although there are no international standards for assessing unmet need, the SAIMS approach permits incremental planning that directs resources at the most important and manageable treatment needs in a population. The simplest procedure is to use population surveys to estimate the number of people in need of treatment (see Ritter et al. 2003; Ungemack et al. 2001). If the rates of dependence and

harmful use are used, these can translate into the potential demand for specialized services (residential and outpatient) as well as early intervention services in other health-care settings. These services can be directed at patients with dependence and harmful use, respectively. Population survey data can be supplemented by obtaining prevalence estimates from settings where substance users are likely to be encountered, such as prisons, emergency departments, HIV clinics, etc. The need for substance abuse services among the general population can also be estimated through the use of health and social indicators, such as substance-related mortality, morbidity, social problem statistics, and expert opinion on treatment needs.

Regarding the latter, the SAIMS includes a qualitative module that provides a way to rapidly collect descriptive information that should be useful to supplement the quantitative data collected in the core instrument or to provide a minimum of information to begin the planning process. The qualitative module requires key informants to collect the information.

78.2.4.3 Needs-Based Planning

For service systems at a modest (Level III) or mature (Level IV) stage of development, it may be more fruitful to conduct "needs-based planning." This approach requires the development of a "model" of the service system and uses population prevalence data to estimate the types of treatment services to be received by subgroups in the population. As such, it is more advanced than the SAIMS methods because it takes into account different types of treatment and respective "need" by treatment type. Two examples of innovative planning methods come from Canada and Australia.

In the Australian project (Ritter et al. 2013), a procedure was developed to provide health planners with estimates of the gap between current service provision and best practice service provision. This planning tool takes into account the epidemiology and severity of substance use disorders, as well as treatment seeking and best practice care pathways.

Epidemiological data are used to derive prevalences of five substance use disorders, and probable cases are apportioned to categories of severity. Expert opinion and a literature review of best practices were used to determine care pathways by drug type and age group for Australia. The model specifies care by drug type, by severity of presentation, and by age ranges. The resulting model is capable of predicting resource use in an optimal alcohol and other drug treatment service system.

In the Canadian project (Rush et al. 2013), the need for treatment is based on five categories of problem severity derived from national survey data and levels of probable help seeking that are projected from a narrative synthesis of international literature. A pan-Canadian Delphi procedure was employed to allocate this probable help-seeking population across an agreed upon set of treatment service categories, which includes three levels each of withdrawal management, community, and residential services. The planning model also includes consideration of screening, brief intervention, and referral to treatment from generic services and placeholders in the model for innovations with respect to interventions based on the Internet and

mobile technology. The resulting capacity projection for each heath planning area in the country can be contrasted with current treatment capacity to yield an estimate of the treatment gap.

78.2.4.4 Mutual Help Organizations

Alcoholics Anonymous and other mutual help organizations represent a critical resource both in countries with mature systems and in those with limited resources. Not only do these approaches provide continued support in the community, they do so at minimal cost. A variety of mutual help models have been developed throughout the world (Humphreys 2004), many of them seemingly capable of managing some of the most difficult cases of drug and alcohol dependence. With an estimated 2.2 million members affiliated with more than 100,000 groups in 150 countries, AA is by far the most widely utilized source of help for drinking problems in the world (Humphreys 2004). Related organizations have been developed in a number of other countries, such as Danshukai in Japan, Kreuzbund in Germany, Croix d'Or and Vie Libre in France, Abstainers Clubs in Poland, Family Clubs in Italy, Links in the Scandinavian countries, Pui Hong self-help organizations in Hong Kong, Oxford House in North America and Australia, and Narcotics Anonymous worldwide (Babor et al. 2010; Humphreys 2004; White 1998).

Although it is regarded as one of the most useful resources for recovering alcoholics, the research literature supporting the efficacy of AA is limited (McCrady and Miller 1993). Attendance at AA tends to be correlated with long-term abstinence (Timko et al. 2000; Humphreys 2004), but this may reflect motivation for recovery. Several large-scale, well-designed studies (Ouimette et al. 1999; Walsh et al. 1991) suggest that AA can have an incremental effect when combined with formal treatment, and AA attendance alone may be better than no intervention. When AA is combined with a 12-week individual therapy called Twelve-Step Facilitation (TSF), one study (Babor and Del Boca 2003) found that TSF not only increased affiliation with AA, it also had a demonstrable effect on clients whose social networks contained many drinking companions. This study suggested that AA is effective because it helps to change the drinker's social environment rather than through some form of spiritual conversion.

78.3 Conclusion

Treatment systems for substance use disorders are a significant part of national responses to the burden of disease and disability resulting from substance abuse. In well-resourced countries, a relatively integrated system of services has been developed in response to population needs. In less-resourced countries, treatment services are often inadequate and fragmentary. Regardless of development level, appropriate population health-care management requires the allocation of resources to preventive, curative, restorative, and rehabilitative services, using the most effective and efficient evidence-based practices. By organizing service providers

into networks, it should be possible to shift utilization to lower cost settings or the most appropriate level of care.

A system-wide holistic approach to the planning and coordination of services for substance use disorders is more than the mere sum of gains attributable to discrete interventions and technologies, such as new screening tools, better diagnostic instruments, improved intervention techniques, and more numerous services. The systems approach goes beyond capacity building and technical innovation. It is designed to coordinate services so that they are capable of responding to the changing needs of the population.

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An Integrated Approach to the Treatment of Drug Dependence: The English Experience

79

Alex Stevens

Contents

Abstract

This chapter focuses on the English experience of developing integrated drug treatment services. It discusses the principles that underlie an integrated approach to the treatment of drug dependence, presents possible methods for integration, and argues that there is no inherent conflict between providing services that both keep people alive through harm reduction and help them to overcome dependence. Treatment services can maximize the benefits that they offer by providing a coordinated continuum of care that ranges from low-threshold harm reduction services to higher-threshold services that give service users the help they may need to make lasting changes to their patterns of dependence and to achieve abstinence. Evidence-based principles that may help people move along this continuum are presented.

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79.1 Introduction

79.1.1 The Need for Integration

At the birth of the current international regime for the control and regulation of illicit drugs, in Article 38 of the 1961 *Single Convention on Narcotic Drugs*, states committed themselves to the creation of a system for the "identification, treatment, education, aftercare, rehabilitation and social reintegration" of drug users. More than 50 years later, we have much more knowledge about what the elements of such a system should be. But debate continues on the best way to coordinate such services. Specifically, it is often suggested that there is an inherent conflict between providing low-threshold, harm reduction services and high-threshold, abstinence-based treatment. This debate has been long running in the UK, but pragmatic solutions have been found to integrate services. These solutions are varied across the countries of the UK. This chapter will focus on the English experience.

It will discuss the principles that underlie an integrated approach to the treatment of drug dependence, will present possible methods for integration, and will argue that there is no inherent conflict between providing services that both keep people alive and help them to overcome dependence. This discussion has two starting points. One, which is often debated, is the evidence that is available to inform the development of treatment systems. The other, which is more rarely discussed in the academic literature, is the normative basis for decisions on treatment provision. Both will be discussed here. This chapter draws on earlier work completed for the Beckley Foundation (Stevens et al. 2006) and more recent research.

79.2 The Integrated Approach

79.2.1 Evidence-Based Services for Dependent Drug Users

The evidence in this area has been repeatedly distilled by distinguished agencies and researchers, including the World Health Organization (WHO), the US National Institute on Drug Abuse (NIDA), the UK National Institute for Health and Clinical Excellence (NICE), the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), and the United Nations Office on Drugs and Crime (UNODC). A useful summary of this evidence base has been provided by Babor et al. (2010). The interventions that they list as being supported by the evidence can be split into two categories, depending on how much commitment to change they require from the drug user. Effective low-threshold services, which tolerate continued drug use, include opiate substitution treatment (with substitution by methadone, buprenorphine, or heroin), needle exchange programs, naloxone distribution for the prevention of fatalities in overdose, and brief interventions in medical settings. Higher-threshold services, which require more commitment to change, include various forms of psychosocial treatment (including outpatient and residential services) and involvement in peer self-help organizations, which often demand

a commitment to abstinence. It is noteworthy that this list does not include detoxification. This is because detoxification, on its own, is not sufficient to support behavior change. Indeed, a significantly increased risk of death has been observed in the period immediately after discharge from detoxification.

This observation, with many others, has informed NIDA's (2012) principles of drug addiction treatment. These also support a range of programs, including abstinence-based and medically assisted treatments, and insist that treatment should be readily available and accessible. A meta-analysis of US studies which relate to these principles (Pearson et al. 2012) supports the majority of them but finds that two NIDA principles which tend to restrict treatment variety (i.e., that treatment outcome is related to length of time in treatment and that treatment should be supported with regular drug testing) are not supported in the meta-analysis. This, again, is consistent with the view that a wide range of treatment modalities can be effective for different people at different stages of their engagement in drug use.

Another form of treatment is missing from the many lists that are available of effective drug treatment. It is compulsory treatment. While NIDA and others suggest that some forms of coercion are not incompatible with effective treatment, this relates to situations where drug users have a constrained choice to enter treatment or to face some other sanction for drug-related crimes. In contrast, programs which compel drug users to enter treatment with no possible alternative – a form of treatment which is prevalent in China and countries of Southeast Asia – have very poor records of effectiveness (in addition to the abuse of human rights and medical ethics which they entail).

79.2.2 The Normative Basis for Service Integration

As Babor et al. (2010) note, judgments on effectiveness of drug treatment depend crucially on the intended outcomes of that treatment. If the aim is to reduce the transmission of HIV and other blood-borne viruses (BBVs), then harm reduction services like needle exchange and opiate substitution treatment may be considered to be most effective. But if the aim is to reduce the prevalence of drug dependence, then treatments which promote abstinence may be judged to have better outcomes. But does providing services to people while they continue to use drugs necessarily conflict with the aim of supporting people to move away from drug dependence? Both the codified standards of human rights and philosophical principles of rationalist ethics (Stevens 2011) would suggest that it is coherent – and even rationally and legally necessary – to provide both harm reduction and abstinence-based services. Pharmacological and other harm reduction services can be provided in ways that support the autonomy of drug users when it has been impaired by addiction. This can be the beginning of a process of recovery and reintegration, not a competitor to it. The right to life is paramount. Services that keep people alive while they are not ready to move away from drug use can also provide a gateway to treatments that can help them define and succeed in their own recovery.

79.2.3 Overcoming the Challenge of Integration

Beyond debates around the evidence base and ethics for integrating services, there are also practical and logistic challenges. These include financial, systemic, and political barriers. Financially, it is likely that different services will be competitors with each other for a slice of the limited budget that is available for the treatment of drug dependence. Money spent on one service is not available to be spent on another. Systemically, it may be very difficult to coordinate services that are managed by different organizations. There may be gaps between services that are run by ministries of health and the criminal justice agencies (e.g., police and prisons) which have most contact with people who are affected by drug dependence. There may be fragmentation and gaps in communication between providers of different services, even when the same individuals are accessing those services simultaneously. Politically, it may be very difficult to generate the support necessary to provide high-quality, integrated services to a group of people who are often marginalized and stigmatized.

Treatment agencies in the UK and elsewhere have increasingly responded to this challenge by pointing to the excellent financial return that drug treatment provides to public investment. Estimates of this vary, and are based on less-than-perfect methodologies, but consistently suggest that treatment provides benefits to society that are of greater monetary value than its costs (e.g., Doran 2008). This enables supporters of treatment provision to argue that investment should be increased, at least until the point where the marginal cost of increasing treatment exceeds the marginal benefit to be gained from it. But there are problems with this approach, besides the need to test these estimates with improved methodologies. One is that the benefits of drug treatment do not always return to the agency that pays for it. For example, much of the benefit of drug treatment is estimated to come in the form of reductions in criminal victimization. The National Treatment Agency for Substance Misuse (NTA, the agency that coordinated drug treatment in England from 2001 to 2013) estimated that £1 million invested annually in drug treatment prevents 9,860 drug-related crimes, with an associated benefit of £1.8 million (NTA 2012). But half of these benefits accrue to potential victims of crime rather than to the state system that pays for the treatment. On the other hand, reduced crime is not the only benefit to arise from drug treatment. An as yet unpublished report by Public Health England (PHE, which took over responsibility for drug treatment from the NTA in 2013) has estimated that the cost of drug treatment per quality-adjusted life year is well above the threshold that is usually used to judge whether investment in a health intervention is worthwhile. However, politicians, despite the desires of many policy analysts, do not make decisions solely on the basis of cost-benefit studies. They have electorates and other parties to satisfy, as well as their own normative preferences to express. Investing money and political capital in the issue of drug dependence may not meet these needs. Perhaps a more politically palatable argument in financially straightened times is that service integration offers ways to save money within the budget that is currently devoted to drug treatment. By reducing duplication of effort,

drug-related deaths, BBV transmission and relapse, integrated services can save money as well as lives.

During years of economic growth, England saw a huge expansion in drug treatment provision between 1998 and 2008. This was delivered through partnership boards, known as Drug Action Teams. These included a range of agencies, such as local authorities (especially housing, youth and social service departments), police, education, and health services. The aim was to develop a more coordinated approach to drug treatment provision. Initially, Drug Action Teams focused on increasing the capacity of methadone maintenance services. But attention has more recently turned to assisting people to leave treatment with their dependency behind them. The current UK drug strategy, published in 2010, recognizes the importance of opiate substitution treatment (including heroin-assisted treatment) but also acknowledges the importance of psychosocial therapy, as well as support for stable housing and employment, in order to help people achieve their aims to live free of dependence.

Another feature of the English system in recent years has been integration between health and criminal justice services for problematic drug users. The government has introduced a growing range of measures to encourage people who have committed crimes and who have problems with drugs to enter treatment. These have ranged from the arrest referral schemes of the 1990s, through the 1998 Drug Treatment and Testing Order (DTTO, a court order which required offenders to enter treatment on a quasi-compulsory basis; the alternative being the usual punishment for the crime), the replacement of the DTTO in 2005 by the Drug Rehabilitation Requirement (DRR), drug testing on arrest, required treatment assessments for those who test positive, and, more recently, alcohol treatment requirements. These have been coordinated through the Drug Interventions Programme (DIP), a centrally funded system of case management that funded workers to build links between criminal justice and treatment agencies. In prisons, the Integrated Drug Treatment Programme has led to a significant expansion of opiate substitution programs, with the aim of reducing the very high rates of death from overdose that have been observed among opiate users in the first few days and weeks after release (Farrell and Marsden 2008). The integration of services has been assisted by the National Health Service taking responsibility for health services in prison (away from the Prison Service itself) in 2003.

When Public Health England replaced the National Treatment Agency in 2013 as the organization responsible for the coordination and integration of drug treatment, the scope for partnership widened. Drug Action Teams have been subsumed into local Health and Wellbeing Boards. The budget for drug treatment has been given to local Directors of Public Health, who are expected to commission services for drug dependence alongside other public health priorities, including alcohol, smoking, violence, communicable diseases, sexual health, and child poverty. This offers the prospect of deeper integration between services but also threatens the budget for drug treatment, which is currently bigger than that for other public health services and may be shifted to these other issues.

England is also moving toward an untested model for the financing of integrated, outcome-focused services for problematic drug users. The idea of the "Payment by Results" approach is that the state will pay service providers for the outcomes that are achieved by the drug users with whom they work. The intention is to create incentives for service providers to deliver outcomes that are both valued by service users and cost-effective for the government. As Humphreys and McLellan (2011) have noted, this strategy is ambitious but untested. Other systems that have attempted to reward service providers principally on the basis of outcomes have been plagued by perverse incentives. One example is the practice of "cherry picking." This happens where the service provider chooses to focus efforts only on those clients who already have the best possibility of achieving outcomes which trigger payments. This creates profit for the service provider but no commensurate benefit to the state or to more problematic clients who may be "parked" and receive little support. Current pilots in England will give more information on the effectiveness of Payment by Results in drug treatment. However, the emerging indications from the application of similar models to services for both unemployed persons and people with criminal convictions are not encouraging.

There is an emerging literature on methods that may help people enter, stay in, and depart from treatment successfully. These include assertive outreach (borrowed from the field of mental health), contingency management (using financial and other incentives to reward retention and progress in treatment), and various forms of case management. However, none has so far proved that it offers a consistently effective approach across different places and target groups. We perhaps have a clearer idea of what does not work. We know that the public stigmatization of drug users does not support abstinence or treatment entry (Palamar et al. 2013; Radcliffe and Stevens 2008). We know that ending treatment prematurely increases risks of death (Hickman et al. 2011). We know that the absence of "recovery capital" (including stable relationships, housing, and employment) is associated with worse outcomes (Laudet and White 2008). Taken together, the evidence suggests that – despite some gaps that need to be filled by more research – we do already have knowledge that we can use to provide integrated services that are able to attract, retain and assist people who have problems with drugs.

79.3 Conclusion

The increasingly integrated English system – at least by the account of the agencies which coordinate it – has been successful in producing health and crime reduction benefits through increased investment in drug treatment; benefits that far outweigh the cost of this investment. There have been encouraging reductions in the estimate of people who have problems with opiates and/or crack cocaine (Hay et al. 2011). But the provision of treatment alone is not sufficient for all treatment entrants to achieve good outcomes. Social dislocation, unemployment, and a lack of stable housing present barriers to the achievement of independent, crime-free lives.

Treatment services can maximize the benefits that they offer by providing a coordinated continuum of care that ranges from low-threshold services – which help to keep people alive while they attain stability – to higher-threshold services that give them the help they may need to make lasting changes to their patterns of dependence. There are evidence-based principles that may help people move along this continuum. These include optimal, sufficient doses for those in medically assisted treatment, as well as the provision of "phased, layered" treatment that supports optimism that people can achieve abstinence (Recovery Orientated Drug Treatment Expert Group 2012). This British report also notes that it is normal for dependent drug users to go through several cycles of drug treatment before they achieve abstinence. Coordinated systems should therefore not disadvantage drug users who have previously "failed" in treatment but should instead offer supportive routes back into treatment. They should recognize that some drug users may not wish or be able to achieve abstinence from their drug of dependence and should provide medical assistance to all categories of drug user. A successful coordinated system is likely to be one that provides a range of points of entry to treatment, a range of options and modalities of treatment and clear pathways between treatment types (e.g., from criminal justice to community services, from detoxification to aftercare, from harm reduction to abstinence – and back again if necessary). Finally, they should provide support for integration into the kind of stable housing and employment which we all need to make good lives.

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Addiction Assessment and Treatment Planning: Developing Countries

80

Nicolas Clark and Ambros Uchtenhagen

Contents

Abstract

Lower-income countries sometimes have difficulties assessing the nature and scope of addiction problems in their countries and in planning the treatment system accordingly. Adapting existing services to changing patterns of substance use disorders and related problems can also be a challenge. This chapter provides a public health approach to the development of a health-care response to drug problems, mainly based on the experience of the World Health Organization working with lower-income countries to assess and develop their drug treatment systems. Options for assessing the need for substance abuse treatment, the nature and extent of available resources, and the functioning of existing services are

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presented, including an assessment of treatment effectiveness and interactions with the criminal justice system. A detailed example of how to proceed is the WHO project on Substance Abuse Instrument for Mapping Services (SAIMS). A range of useful tools for treatment planning and a checklist on standards of care in addiction treatment are presented in the appendix.

80.1 Introduction

The addiction medicine specialist is often called upon to advice on the development of treatment systems. While Chap. 81, "Screening and Assessment for People with Substance Use Disorders: A Focus on Developed Countries" in this section advises on the issues in higher-income countries, this chapter gives a guide to the development and organization of services in lower-income countries.

According to the WHO ATLAS survey (WHO 2011), lower-income countries typically have less medical staff, less services, less funding reserved for addiction care, and less care provided for special populations like adolescents or prison inmates. Some countries may find themselves with few addiction medical specialists, or in some cases none. Few staff will likely have training in structured psychological techniques.

Funding for health services may be from specific donors such as The Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), or may require out-of-pocket contributions which put it beyond the reach of most of those who needs them.

The last 50 years have seen some dramatic changes in the patterns of substance use and related health and social problems, and in many countries, the health-care systems, which often predate these changes, struggle to respond. This is particularly the case in lower-income country settings. Growing wealth and development leads in many cases to a rapidly developing health-care system and brings with it the chance for significant rethinking and reorganization of the health-care system response to substance use and related problems such as HIV, TB, and hepatitis and social problems such as poverty, malnutrition, unemployment, homelessness, and crime.

This chapter is an outline of a public health approach to the development of a health-care response to substance use disorders and related health and social problems, with a particular focus on lower-income countries, based largely on the experience of the World Health Organization work in such countries.

80.2 Planning Steps

80.2.1 Step 1: Defining the Problem (Treatment Need)

It may be the case that there is no good data on the local epidemiology of substance use disorders and the corresponding demand for treatment. In this case a stepwise approach to understanding the problem is proposed. While data on substance use is an important consideration, it is the prevalence of substance use disorders, in particular substance dependence and associated physical and psychiatric disorders, which is the better guide to treatment need.

80.2.1.1 Basic Approach

- ***Check sales data.*** For substances which are legally traded, as is the case for alcohol in most countries, statistics or estimates on national per capita consumption are available either from national sources or from the WHO Global Health Observatory (WHO.int/gho). For illicit drugs it can be more difficult to determine the extent and patterns of substance use disorders.
- ***Ask your patients***. The most basic approach to determining the nature and extent of substance use problems in a country is to ask the patients of different health-care facilities. Addiction specialists practicing in the country can ask their patients not just what substances they are using but also about the availability of substances, the recent trends in the availability of substances, and with which substances the patient has seen other people developing problems with. Asking your patients if it is difficult to get into treatment, i.e., if there is a long waiting list and what proportion of the people they know with substance use problems have received treatment, can be a basic indication of the unmet demand for treatment. If you are a visiting consultant, it is usually possible to ask if you can have an informal conversation with a number of patients.
- ***Ask other people about their patients.*** The next step is to ask other health-care staff about their patients, in the facilities which tend to attract patients with substance use disorders. Ask psychiatric facilities what substances the mental health patients are using; on what substances are people presenting for overdose; with what patterns of substance use are people presenting to the emergency department; what substance use patterns are NGOs providing harm reduction services for drug users seeing; what proportion of HIV patients are injecting drugs, drinking heavily, or using other substances in combination with risky sexual practices; and what proportion of liver patients have hepatitis C, are heavy drinkers, and so on and so forth.

80.2.1.2 Intermediate Approach: Routine Data Collection and Fieldwork

- ***Ask people on the street***. This can be done most easily by engaging a "peer worker," someone who is or who has been in the same situation as the people on the street and with whom you can have a good working relationship.
- ***Analyze data collected from other health-care facilities***, such as drug treatment centers, psychiatric hospitals, emergency departments, and HIV treatment cohorts. Other parts of the health-care system may be collecting data that could be used to indicate what problems there may be due to drug use in the community, such as rates of HIV and hepatitis, the proportion of new infections of HIV and hepatitis that are related to injecting drug use, emergency department presentations due to alcohol, etc. If such data are not currently being collected, it may be possible to introduce one or two key indicators into the routine data collection in these facilities, depending on the circumstances. Ask to see what data they collect, and see if there is a template which can be modified slightly to collect useful data and if there is a way that data can be shared in a way that protects the privacy regulations and confidentiality of the people involved.
- ***Look for data from other sectors*** such as police, prisons, and customs. Data from other sectors can also shed a light on the nature of the drug and alcohol

problem in a community. The type and amount of drugs seized by customs may be publically available in a report. The prison may collect data on what drugs people are using when they come into prison. The police may keep records on what drug-related arrests are made, or the number of people charged for driving while over the legal limit for alcohol.

80.2.1.3 Advanced Approach: Systematic Data Collection

Epidemiological Estimates of Drug Use Disorders and Associated Health Conditions

A detailed description of the various epidemiological techniques for assessing the treatment need is beyond the scope of this chapter, and the reader is referred to Chap. 4, "Burden of Disease: The Epidemiological Aspects of Addiction", Sect. 1 of this textbook. There are a number of points that are worth keeping in mind, however. Firstly, remember that it is the patterns of substance use that are causing the most harm, not prevalence of drug use, that are likely to better correspond to treatment need. People who have used cannabis in the last 12 months, for example, meet most definitions of "drug use" but rarely attend for treatment. Daily patterns of substance use are more correlated to dependence and therefore also treatment need. Secondly, there are some newer techniques for drug epidemiology that are worth considering. Wastewater analysis can be a quick and cheap way to monitor trends in drug use in a city with a wastewater plant. If there is no facility to conduct the analysis in the country, then it can be easily sent by mail to a laboratory that specializes in such assessments (EMCDDA 2008). In communities with high uptake of mobile phones, and where there is a list of mobile phone numbers, or where a random phone dialer can be used to generate a random sample of people in the community, it may be worth considering the network scale-up approach. This approach is based not on the substance use patterns of the person being interviewed but of the other persons in their network of friends and associates. Then by also estimating the size of that person's network, this can be a shortcut to estimating the prevalence of rare or stigmatized behaviors.

Surveys of drug use in school and university students, while not a new technique, can be much easier to conduct than general population surveys and can be conducted often with the assistance of WHO such as the global school-based student health survey (GSHS), which has an optional module on substance use (http://www.who.int/chp/gshs/en/).

80.2.2 Step 2: Look at the Available Resources

The second step is to conduct an inventory of the resources that are currently being used and which could be recruited to tackle the problem of substance use disorders in the country.

This might involve putting together a list of the treatment facilities in the country, including specialized treatment centers and psychiatric facilities with how many staff they have and with what skills.

Treatment facilities can be defined in different ways. The important characteristics to measure are the treatment capacity; whether they are a place where people sleep or not (if yes, the number of beds); the number and qualifications of staff; what medications are available; whether treatment is private, not for profit, or government owned; and the approximate cost of treatment.

Then it is worth noting what services are offered by these treatment services, inpatient and outpatient detoxification, opioid maintenance treatment, counseling, social support, medication for relapse prevention, medical and psychiatric assessment, and treatment of medical and psychiatric comorbidity.

80.2.2.1 What Are the Components of a Substance Abuse Treatment System?

- ***Facilities***
  Hospital beds, nonhospital residential facility (detoxification center, long-term rehabilitation, therapeutic community, supported accommodation), outpatient, and outreach team (few or no fixed facilities). See also Chap. 78, "Treatment Systems for Population Management of Substance Use Disorders: Requirements and Priorities from a Public Health Perspective" of this section.
- ***Human resources***
  Specialist medical, generalist medical, nursing, social work, drug- and alcohol-specific counselors, and lay counselors
- ***Health technologies***
  Medicines, therapeutic techniques, and investigations
- ***Governance infrastructure/financing***
  Government ministry(ies), mechanism of decision making between different parts of the government, public, private, and insurance
- ***Information***
  National substance use observatory, epidemiology, trends, research, and information system
- The ***broader components of a substance abuse treatment system*** include other elements of the health-care system, including the mental health treatment system, drop-in centers, needle and syringe exchanges, and prison health system.
- ***Other systems to which the treatment system relates*** include police, criminal justice, employment, housing support, the social support systems, mutual support organizations, nongovernment organizations, and faith-based organizations.

80.2.3 Step 3: Assess the Functioning of the System

The next step is to consider the functioning of a treatment system. Is treatment available, accessible, affordable, acceptable, of good quality, adequately used, and providing continuity of care? Does treatment adhere to legal and ethical standards of patient care? Do the different components of the treatment system communicate and articulate effectively? Again, this assessment can be made either from

discussions with patients, colleagues, patient representatives, and family members or by more formal data collection such as anonymous questionnaires on treatment quality and measures of treatment effectiveness.

80.2.3.1 Current State of Health-Care Systems

Data from the WHO ATLAS survey (WHO 2011) on the organization of health-care systems for responding to substance abuse highlight that there is no one model of the substance abuse treatment system. Approximately one third to one half use their psychiatric systems, one third have special systems, and the remainder the general health-care system, or sometimes even the criminal justice system plays a role. Regional information systems on Africa, Asia, and Europe are available (WHO.int/gho/substance-abuse/treatment/en/index).

Common problems of drug treatment systems are:

- The ***size of the health-care response is inadequate*** compared to the burden of disease. Often drug treatment systems are only treating a small proportion of those in need, usually due to lack of funding. In many cases, health financiers have been convinced by health economic analyses that it saves the country money in lost productivity, health-care costs, and criminal justice costs to fund substance use treatment at a higher level (NHS 2012; UNODC 2003).
- The ***lack of a home for substance abuse within the health-care system***. The lack of a coherent substance abuse treatment system makes the development of the system difficult, particularly if the place where the treatment is based does not see substance abuse as part of their core business. Whether it is in psychiatry or as a separate entity, having a recognized focal point within the ministry of health, within academia, and within the public health system is vital to improving substance abuse treatment. In many countries this does not exist, as the treatment of substance dependence is a relatively new speciality, and it has developed wherever anyone has shown an interest. While this can be good to get things started, in the long run it is usually necessary to get the political support that is needed to run drug and alcohol treatment services to have a clear focus for those services.
- ***Accessing treatment of medical comorbidities*** such as HIV and TB is a key issue, particularly in the treatment of heroin dependence. The model of receiving the treatment of heroin dependence (with methadone or buprenorphine maintenance) at the same time as receiving the HIV +/− TB medication has shown to be very effective in facilitating good adherence to HIV and TB regimens. Ideally the same pharmacist can provide all three medications at once, and then the patient can also get whatever psychosocial support that they need at the same time. Such models have been set up in many low-income settings around the world (including countries in Africa, Asia, Eastern Europe, and the Middle East) and are the key to improving the very low rates of treatment of HIV in people who inject drugs. In order for such treatment methods to work, sometimes an HIV specialist needs to learn drug treatment, or a drug treatment specialist needs to learn how to treat HIV, or they both need to learn to work together. In any case, such a simple strategy is often difficult to implement in rigid bureaucratic environments.

- ***The role of primary health care***. Almost certainly, it will soon be clear that there are not enough specialist staff to treat all the patients with substance use disorders in the country. The addiction medicine specialist then needs to decide whether or not to allocate some of his or her time to building the capacity of primary care services to manage people with substance use disorders. Most people with substance use disorders already are engaged with a primary care service. Discharge from hospital, detoxification, or other substance misuse service can be an occasion to contact that primary care service and encourage them to continue the care that has been started, particularly if there is a clear role such as the prescription of relapse prevention medication. Primary care services are often happy to collaborate with specialist care services, as long as those specialist services will be able to support them with a difficult patient when the time comes.
- ***The lack of key pharmacological responses***. Despite being around for many years, many services do not provide methadone or buprenorphine treatment. Medication for relapse prevention from alcohol dependence is also often not available. The use of such medication greatly enhances the effectiveness of the service and is a must for any addiction service.
- ***Competing models of care in the criminal justice sector*** including compulsory treatment. Despite substance dependence being a health condition, sometimes treatment is provided by services under the responsibility of the police or justice ministries. Even when the person is in prison, the health-care treatment should be provided under the auspices of the ministry of health.

80.2.3.2 Matching the Treatment System to the Needs

- ***Size and shape*****:** is there proportionate amount of investment overall and in the different components? What treatment services are required? How many specialists, generalists, doctors, nurses, pharmacists, etc.? In the absence of detailed epidemiological data, how can planners know the ideal treatment capacity for their health administrative region?

  For each 500,000 population, a high-income country will typically have (either provided by government, NGO, or private):
  - 10–15 detoxification beds
  - A consultation liaison service that sees patients in the hospital(s) with substance use disorders
  - Three to six addiction specialists
  - Outpatient treatment
  - Psychosocial support
  - Needle and syringe exchange, outreach, and other harm reduction services

  Combining the sources of data should enable a picture of the untreated treatment need to come forward:
- ***Alcohol dependence***

  Need for medical detoxification services, relapse prevention with psychosocial support and medication, and self-help

- ***Binge alcohol use***
  Screening and brief interventions in emergency departments and primary care and referral of the more severe cases to treatment
- ***Heroin dependence***
  Opioid maintenance treatment with methadone or buprenorphine. Psychosocial support and access to sterile injection equipment, HIV and hepatitis testing and treatment, and +/− TB screening and treatment

80.2.3.3 Assessing Treatment Quality

Treatment quality is essential for the acceptability of addiction treatment to patients, to staff, and to the general public, and it is essential for reliable good outcomes.

When you want to assess the quality of treatment services or a service network, the following questions are helpful to identify weaknesses and areas for quality improvement:

- Is there a clear concept about objectives and methods to be used?
- Have staff been trained how to use the therapeutic methods, and do staff get continued education about new evidence on those methods?
- Are staff aware of their respective duties and responsibilities (e.g., are there written procedures and guidelines)?
- Are staff attitudes towards addiction problems and patients favorable?
- Are there good working relationships with other services (e.g., somatic, psychiatric, social)?
- Is the workload of staff acceptable?
- Are the locations and infrastructures of services adequate?
- Are the human and financial resources of services adequate?
- Are services known and acceptable for the target population?
- Are patients satisfied with the treatment they receive?
- Are services accepted by other professionals and in the community?
- Does addiction treatment have adequate political support?
- Is there a system of clinical accountability within the service (in other words, is there someone whose responsibility is to ensure the standard of quality within the service, and to whom other staff must be accountable)?
- Are adverse events documented and discussed regularly?
- Are patients given the opportunity to contribute to the development of the service?

It is highly desirable to use multiple sources of information to find answers to these questions, including staff in various functions, patients and former patients, family members of patients, nontherapeutic services caring for addicted patients, family doctors and hospitals, and law enforcement. When identifying weaknesses and deficits, continue to ask how these could be improved.

In addition, it should be clear that services for the treatment of substance abuse problems are in line with legal requirements for health and social care, as well as with ethical guidelines if available for health and social care.

For a systematic checking of service quality, the WHO questionnaire on standards of care is a useful instrument (WHO 1993). The intention is to look at how adequately the treatment needs of a population are being served. For each standard, it should be checked if it is in place and in adequate form and if not how the situation could be improved. A checklist based on these standards of care can be found in the Annex. There have also been attempts to use business principles to assess and improve treatment quality and efficiency, including a walk-through of the treatment service and looking at the service from the consumer perspective (Ford et al. 2007; Quanbeck et al. 2012).

80.2.3.4 Assessing Treatment Effectiveness

Treatment effectiveness can be measured at different levels: intervention, service, and system (network of services) level. Effectiveness is usually measured by determining treatment outcomes, regarding health status, type and amount of substance use, social integration, and quality of life of patients (EMCDDA 2007, see also Chap. 88, "Monitoring and Evaluation of Addiction Treatment" in this section). Measurements can be made by the degree of goal attainment (reaching a predetermined outcome), or by the nature and size of change in the abovementioned domains.

Effectiveness of ***special treatment approaches and methods (intervention level)*** is measured in clinical trials. Outcomes of such trials are compared in reviews or meta-analytic studies, providing information on the probability of positive results for which drugs, which patients, in which settings, and under which circumstances (EMCDDA 2007). For an assessment of special approaches and methods in your services, you will need to collect baseline and follow-up data, in order to determine change during treatment. It is also worth considering a randomized clinical trial, particularly if you have a significant volume of patients, as this reduces many potential sources of bias that may otherwise make it difficult to interpret the results. In either case, standardized instruments are available for this purpose (WHO/UNODC/EMCDDA 2000; EMCDDA evaluation instrument bank EIB).

Effectiveness of ***treatment programs and services (service level)*** is determined by measuring the same outcome indicators for all patients enrolled in a treatment program or service for a specified period (e.g., annually or biannually). This is made by collecting routinely selected outcome data (monitoring) or by implementing an evaluation research project. Examples for both can be found in the WHO evaluation workbooks (WHO/UNODC/EMCDDA 2000). A useful indicator for service effectiveness is the rate of regular discharges after treatment termination in contrast to premature dropping out and discharge; another is the rate of relapse following discharge (see also Chap. 88, "Monitoring and Evaluation of Addiction Treatment" in this section). Self-evaluation of services needs to be kept to a minimum of data and not measured more frequently than every 3 months. External evaluation is preferable to avoid bias.

Effectiveness of a ***treatment network (system level)*** does measure how well treatment needs in a given country or region are taken care of by the available services (coverage). This is done by comparing the estimated number and type of

substance abuse problems with the documented number and type of treatment populations. A simple method is a routine documentation of waiting lists and waiting time, although those also depend on the quality and acceptability of services. If there is no formal waiting list, new patients can be asked how easy it was to access the service. In addition, satisfaction of treatment populations and other stakeholders is a good indicator for satisfactory outcomes.

80.2.3.5 Interaction with the Criminal Justice System

Legal conflicts and criminal involvement are frequent consequences of substance abuse. The range goes from driving under the influence and violation of traffic rules to property crimes to domestic or public violence, not to mention the involvement in dealing with illegal drugs.

In some countries, such cases can be dealt with in special courts (e.g., drug courts) which can mandate treatment instead of imprisonment (Perry et al. 2008, Mitchell et al. 2012). In many countries, all criminal courts have the possibility to propose treatment instead of imprisonment (if indicated and with patient's consent) (Stevens et al. 2005). Treatments can be provided in regular community-based services, or in special prison institutions. Research has shown that in-prison drug-free residential treatment (therapeutic community type) has good outcomes if including a reentry phase with continued therapeutic contact (Mitchell et al. 2006). The same has been demonstrated for opioid maintenance treatment inside and outside of the prison system (Hedrich et al. 2012; WHO 2009a). Apart from a reduction in addictive behaviors, these treatments result in a remarkable reduction in criminal involvement.

Compulsory referral to reeducation and labor camps without formal treatment and therapeutic staff is not efficient in changing addictive behavior, is followed by high relapse rates to substance abuse and criminal involvement, and is ethically not acceptable (WHO 2009b). Also, compulsory forms of treatment in general have poor outcomes, mostly due to lack of motivation for behavior change (Hiller et al. 2002).

80.2.4 Example from WHO Experience: The SAIMS (Substance Abuse Instrument for Mapping Services)

80.2.4.1 Measuring the Treatment System

The objectives of the SAIMS are to support a standardized method for measuring the extent, quality, and integration of services for substance use disorders, including whether current services are meeting population needs; to demonstrate accountability; and to enable planning based on public health considerations rather than ideology, fads, and personal and professional preferences.

Its other objectives are to inform prevention policy, identify emerging drug epidemics, identify pathways to care, identify barriers to services, and describe the gap between existing service configuration and aggregate distribution of substance use disorders in the population.

The scope of assessment includes:
- Treatment services
- Diagnostic services
- Detoxification
- Medical/psychological/social support
- Therapeutic communities
- Self-help
- Primary prevention
- Health promotion
- Secondary prevention
- Harm reduction

80.2.4.2 Treatment Planning Based on SAIMS

A complete approach to a more comprehensive evaluation of a treatment system based on SAIMS includes some additional steps:
- ***Bring together the key stakeholders in drug treatment***. With the government this may include ministries of health and drug control/security/criminal justice. This might mean the establishment or reactivation of mechanisms of interministerial decision making. Often the prime minister's (or president's) office takes the responsibility to look after this committee itself.
- ***Conduct an assessment and description of the treatment system.***
- ***Analyze the fit with population needs*** for substance abuse services, including gaps in services.
- ***Plan new services***, reallocate resources, and train new staff.
- ***Monitor changes*** as system develops.
- ***Compare analysis*** within and across national boundaries.

80.2.5 Planning for Treatment Development

Once the assessment of the gaps between the current treatment system and the treatment need, a plan for sustainable development of the treatment system should be developed. The nature of this development depends to a large extent on the funding available.

In the absence of further funding, it may still be possible to reorient the treatment system to the areas of unmet treatment need. Further development, even if temporarily funded by foundations such as The Global Fund, will ultimately need sources of funding found within the country, either from government or insurance mechanisms. Since this process can take a long time, it is important to start these discussions early.

Any treatment development will need an increased workforce. Inclusion of elements of substance abuse treatment into the major health curricula in the country will increase the capacity across the whole treatment system. In the meanwhile, many existing practitioners can be assisted to provide substance abuse treatment with mentoring and support, even telephone support, and first-hand exposure to substance abuse treatment, either within the country or abroad.

For rapid expansion in treatment capacity, it may be useful to work with NGOs which focus on substance misuse treatment. In the longer term, for substance abuse treatment to be brought to scale, it will probably be necessary to develop such treatment within the public treatment system.

The addiction medicine physician is often in a unique position to contribute to treatment system development: understanding the nature of substance misuse treatment (including the gaps in current treatment), having the skills to train and mentor the next generation of treatment providers, and also having the capacity to influence funders and decision makers about the structure of the treatment system. When there is a shortage of expertise in a country, the addiction medicine physician will inevitably feel torn between providing patient care and nonclinical activities; however there are many opportunities for a public health impact by supporting the development and orientation of treatment systems for substance use disorders towards public health goals.

Appendix

Tools for Treatment Planning

Tool for Mapping Treatment Facilities

1. Type of treatment service (select one):
   - General health service (primary care, district hospital)
   - Mental health (including substance use) treatment service
   - Specialist substance abuse treatment service
   - Alcohol only treatment service
   - Drug only treatment service
   - Other (specify)
2. Service setting (select one):
   - Community
   - Hospital
   - Prison
   - Other closed setting (specify)
3. Facilities (multiple answers):
   - Outpatient treatment
     - Number of rooms for seeing patients/clients
   - Inpatient beds
     - Number of beds
   - Outreach
   - Pharmacy
4. Staff time involved in the treatment of substance abuse (in number of equivalents of full-time staff):
   - Medical staff
     - Addiction specialists (addiction medicine or addiction psychiatry)

    - General psychiatrists
    - Internal medicine specialists
    - Other specialist staff (specify)
    - Primary care physician
  - Nursing staff
    - Addiction nurses
    - Psychiatric nurses
    - General nurses
  - Pharmacists
  - Psychologists trained in substance use disorders
  - Social workers trained in substance use disorders
  - Occupational therapists trained in substance use disorders
  - Ex patients – trained in substance use disorders
  - Other (specify)
5. Services provided (approximate number of patients in each category at any given time – choose the one category that best fits each patient):
  - Assessment/diagnosis
  - Outpatient management of withdrawal
  - Inpatient management of withdrawal
  - Individual counseling
  - Group counseling
  - Opioid maintenance treatment
  - Relapse prevention medication
  - Treatment of comorbidity
    - Mental health problems
    - Wound problems
    - HIV/AIDS
    - Hepatitis/liver disease
    - TB
    - Sexually transmitted infections
  - Sterile injecting equipment
6. Does the service have programs specifically for different populations?
  - Pregnant women
  - Adolescents
  - People with mental health and substance use problems
  - People with physical health and substance use problems
  - Men
  - Women
7. Who is responsible for the treatment center?
  - Ministry of health
  - Other government ministry (specify)
  - NGO/FBO (specify)
  - Private company or individual (specify)
  - Academic institution (specify)

Tool for Minimum Data Set of Patients in Treatment Facilities

central Form code (to be filled at the central level):

Annex 1 Substance use treatment information system - examiner report form

1.1 Form code (to be filled at the data collection centre):	1.2 Patient' unique anonymous ID: [ ]
1.3. Staff ID as used at the facility [ ]	1.4 Catchment area name [ ] Catchment area code [ ]
1.5 Centre name: centre code: [ ]	1.6 Reported waiting period: # of days
1.7 Date of first clinical assessment:	Month | Day | Year
2.1 Age (years):_____	2.2 Sex 1☐ male 2☐ female 9☐ other
3.Source of referral: 3.1 self or individual ☐ 3.2 health system referral ☐ 3.3 criminal justice system ☐ 3.4 other[1]☐ [1]please specify: _____	

4. Type of substance (s) involved in current treatment episode	Primary	Non primary	Specify the name of the substance	5. Route of the administration of *primary substance* involved in current treatment episode	Please tick
4.1 Opioids				5.1 Oral	
4.2 Cannabinoids				5.2 Injecting	
4.3 ATS				5.3 Smoking	
4.4 Cocaine				5.4 Inhaling	
4.5 Hallucinogens				5.5 Snorting	
4.6 Solvents				5.6 Unknown	
4.7 Sedatives/hypnotics				6.History: 6.1 Age of first use of the primary substance (years): _____	
4.8 Alcohol					
4.9 Other					
4.10 Number of days the primary substance was used in the last 28 days: _____				6.2 Is this the first ever treatment episode: *Yes* ☐ *no* ☐	

7. Pattern of use (injection and sharing equipment): 7.1 History of injecting over the lifetime: *Yes* ☐ *no* ☐ 7.2 History of Injecting equipment shared over the lifetime: *Yes* ☐ *no* ☐ 7.3 Any sharing of injecting equipment during the last 28 days: *Yes* ☐ *no* ☐	
8. Treatment setting planned for the current treatment episode: 8.1 Inpatient ☐ 8.2 Outpatient ☐ 8.3 Residential ☐	9.1 Opioid maintenance treatment planned for the current treatment episode: *Yes* ☐ *no* ☐ 9.2 Type of medication to be used for maintenance treatment: Methadone: ☐ Buprenorphine: ☐

Tool for Routine Outcome Data Collection

http://www.nta.nhs.uk/uploads/topformoct13.pdf

Tool for Quality of Patient Care (Quality Rights)

http://www.who.int/mental_health/policy/quality_rights/en/

Checklist on Standards of Care

Standards on Access, Availability, and Admission Criteria

A1	Service is easily accessible with regard to location, travel time, and transportation
A2	Services are obtainable without restrictions of time and day
A3	Treatment is available without delays creating risks for patient
A4	A range of treatment settings and treatment options are available (residential, outpatient, day care)
A5	Services are available without the need to undertake laboratory tests, such as tests for HIV
A6	Services are available irrespective of age and gender
A7	Services are available irrespective of ethnic, political, or religious background or beliefs of patient
A8	Services are available irrespective of the type of drug(s), route of administration, and legal status of drug(s)
A9	Patient may continue with prior established treatment of other conditions without prejudice of access to treatment
A10	Service is available irrespective of the somatic or psychiatric condition of patient (including HIV)
A11	Service is available irrespective of the patient's legal status or of past or ongoing prosecutions (including those related to drug use)
A12	Service is available irrespective of the patient's ability to pay, economic or employment status
A13	Professional services are available in custodial settings (e.g., police cells, prisons)
A14	Service is available irrespective of the current drug use of patient
A15	Service is available irrespective of history of prior treatments
A16	Regular contact exists between specialist treatment facilities and general

Standards on Assessment

B1	An initial assessment is made in order to prioritize interventions in a coordinated treatment plan
B2	An assessment is made to detect complicating physical and neurological disorders
B3	A psychiatric/psychological assessment is made to detect complicating disorders (e.g., depression)
B4	An assessment is made of the social circumstances (e.g., family, employment, housing, financial, and legal position)
B5	Methods for the rapid identification of substances used are available through laboratory tests (e.g., urine or blood) or other procedures
B6	Laboratory facilities are available to assist in the assessment of physical and psychiatric/psychological disorders
B7	Standardized instruments for diagnosis are used (e.g., ICD-10)
B8	Detailed records are kept on assessment results at entry

Standards on Treatment Content, Provision, and Organization

C1	Records of patient management, progress, and referral are kept
C2	Treatments are chosen on the basis of drug use, somatic and mental state, and social circumstances

(*continued*)

C3	Treatments are chosen on the basis of somatic and psychiatric disorders and the social situation of patients
C4	Defined protocols exist for prescribing and other interventions appropriate to the specific needs of patients
C5	The protocols are based in research evidence wherever possible
C6	Patients are informed on the range of available treatment options
C7	Whether or not the treatment goal is abstinence, measures are taken to reduce the harm from continued drug use
C8	The least risk-producing treatments are chosen on the basis of a careful risk-benefit assessment
C9	Home-based treatment is available with regular visits by trained staff
C10	Access to self-help and other support groups is available
C11	Information about 24 h emergency facilities is provided
C12	Patients with overdose receive immediate care in-house or through referral to a well-equipped other service
C13	Continuity of care is assured
C14	There is regular evaluation of the service/program
C15	There are links to other services for the care of children or other family members in need of care and support

Standards on Discharge, Aftercare, and Referral

D1	There are defined criteria for the expulsion of patients due to violation of treatment service rules
D2	There are defined criteria for (unvoluntary) retention of patients (e.g., intoxication, suicide risk)
D3	Discharge is based on determination of patient recovery status and on patient's consent
D4	Referral to other services is offered in case of expulsion/discharge
D5	Referral to aftercare and continued support (e.g., social or family support) is offered

Standards on Outreach and Early Intervention

E1	Primary health facilities are informed about your services
E2	Police and the judiciary system (courts, parole, and probation officers) are aware and informed about your services
E3	Counseling of drug users, family members, employers, and other key persons is available in your services

Standards on Patient's Rights

F1	The Universal Declaration of Human Rights applies in your services and is known to staff
F2	Information about the patient's condition, progress, and treatment involvement is not divulged to anybody without the patient's consent
F3	Patients are fully informed about the nature and content of their treatment as well as the risks and benefits to be expected
F4	Prior informed consent is obtained from patients regarding the content, conditions, and restrictions of treatment
F5	A documented complain procedure exists and is made known to patients and their relatives

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Screening and Assessment for People with Substance Use Disorders: A Focus on Developed Countries

81

Brian Rush

Contents

Abstract

This chapter outlines the rationale for a more proactive concerted effort to screen for and assess mental health problems and at-risk consumption of alcohol and other drugs and related addictions problems given the evidence concerning the level of under-detection in routine practice and the excellent performance of a host of screening tools and processes. When used for clinical decision-making, best practice calls for a staged approach to maximize efficiency of the overall screening and assessment process and ensure a link to subsequent outcome monitoring. While several specific tools are highlighted, the essential principle for service and system planning is that they must be tailored to the setting and target population for which they are being implemented. Whether working in generic settings such as primary care or specialized settings, a collaborative approach, drawing upon multidisciplinary, multi-provider, and multi-sectoral expertise, is needed across the stages of screening and assessment, along with

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a collaborative response protocol for level-of-care placement/referral for treatment and support. The effectiveness of screening is reviewed, and the evidence is quite strong with respect to the ability of screening tools and processes to identify individuals needing brief intervention or other treatment and support. However, the effectiveness literature also tells us that screening is only one part of the process of engagement and the results are more equivocal in terms of the impact of the screening per se on subsequent case management and health outcomes. The literature on SBIRT in the addiction field is an important exception to this finding. Much more research is also needed on the facilitators and barriers to implementing universal or targeted screening and assessment tools and processes at both the level of the individual service provider and within collaborative, shared care arrangements.

81.1 Introduction

The purpose of this chapter is to provide an overview of screening and assessment tools and processes in the context of middle- to high-income (i.e., "developed") countries. In this context, there are important similarities but also differences in the many other books and research papers synthesizing this work from psychiatric (First and Tasman 2006; Greenfield and Hennessy 2008), behavioral (Miller 2006; Tucker et al. 2004), or social work perspectives (Jordan and Franklin 2011). Like previous work, there is an acknowledgement of important principles and practices that can be seen as universal in nature, for example, the need for an evidence-based approach grounded on a comprehensive bio-psycho-social-spiritual model; sensitivity to individual differences in culture, diversity, and developmental age; the critical importance of empathy, listening skills, and therapeutic alliance; and the appropriate involvement of family and significant others. These aspects are critical elements of the interface between clinician and client. Such similarities notwithstanding, this chapter emphasizes more of a systems approach, recognizing that in so-called "developed" countries, the greater resource base offers an opportunity for a collaborative approach to engaging people in need, identifying and assessing their strengths and problem areas, offering a wide range of service options along a continuum of care, and, ideally, following up with post-discharge recovery monitoring. This collaborative approach may involve more than one provider, organization, and service delivery sector – a scenario that professionals working in low-income countries may only dream about in terms of collegial support for their work. Further, many screening and assessment tools that complement clinical skills and experience are not available and validated in many low-income countries. This is another advantage conferred on moderate- to high-income countries that have capacity for research and development.

In short, this chapter acknowledges the value and greater feasibility of a broader systems approach to treatment and support for substance abuse and co-occurring conditions, including screening and assessment (Institute of Medicine 1990). In addition, the underpinnings of collaborative care call for us to aim this chapter

at people working from a range of professional disciplines, for example, psychology, social work, nursing, family practice, psychiatry, and other medical and nonmedical specialists. For this reason, some readers working from an exclusive addiction medicine or psychiatric perspective may benefit from additional discipline-specific, reference texts such as First and Tasman (2006), written for psychiatry. This excellent reference text also provides more details on clinical assessment relevant for particular substances such as alcohol, cocaine, and opiates.

Although there are many important inter-jurisdictional differences in the capacity for screening and assessment, it is important to recognize that many "developed" countries are far from homogonous in terms of community need and capacity to respond. Taking Canada as but one example, there is a tremendous range within the country in terms of rurality/urbanicity, multiculturalism, indigenous versus nonindigenous populations, and substance use patterns and related harms. These and many other factors all influence beliefs about substance use and addiction, the perceived value of treatment, help-seeking behavior, and no doubt cultural interpretation of concepts such as "assessment" or "treatment." There is also wide variation in availability and accessibility of options for treatment and support, an obvious factor critical to screening and assessment considerations. With these caveats in mind, the goal here is to provide guidance to the reader on the screening and assessment of substance abuse risk and harms, primarily from a collaborative care, systems perspective appropriate for many middle- to high-income countries.

81.2 Core Principles and Practices

81.2.1 Rationale for Screening and Assessment

It is widely recognized that only a small minority of people with mental health and addiction-related concerns seek help from either community professionals or less formal services (Urbanoski et al. 2007; Kohn et al. 2004). Reasons behind this are many and varied across communities, including limited access to services or just not knowing how/where to seek help; stigma and discrimination that challenge people to seek help or that impact the attitudes and behavior of the helping agents they encounter; feeling able to manage on their own; and personal challenges related to such responsibilities as work, school, and childcare (Sareen et al. 2007; Urbanoski et al. 2008). Considerable research has also informed us for some time that, among those who seek help, the largest proportion will access a primary health-care provider or other health and social service professional (Shapiro et al. 1984; Kessler et al. 1996; Urbanoski et al. 2007). Although many people with mental health and addiction-related problems, or who are at risk of such problems, are in contact with various service providers, these risks or problems are often not identified (Barnaby et al. 2003; Weaver et al. 2003; Mitchell et al. 2012). These contacts are "teachable moments" and as such are missed opportunities for offering advice, more extended consultation, or referral for additional support.

The focus on improved screening and assessment is a critical element of efforts to "broaden the base" of treatment through a service delivery network that extends well beyond the traditional specialized sector of addiction services (Institute of Medicine 1990; Babor et al. 2008). In particular, there is a need to bring addiction specialists together with primary care physicians and professionals in other health-care settings and community services to deliver collaborative, shared care (e.g., Druss and Mauer 2010; Ivbijaro 2012; Chalk et al. 2011). Models of collaborative mental health care, including addictions, significantly extend the reach of the community-based treatment and support system.

The above trends in service delivery highlight the importance of generic community services such as primary care, hospitals, social services, schools and other education settings, and justice-related services being proactive in asking questions about mental health, substance use, and addiction-related issues in order to identify concerns, increase opportunities for early identification, provide access to more in-depth assessment and other services and supports, and link the person to more specialized services when needed. For people with low-to moderate risk, or less severe mental health and addiction problems, engaging in proactive, opportunistic screening and on-site brief intervention is intended to reduce risks and harms and have a positive impact on health-related outcomes. For those with higher risk, or more severe and complex problems, opportunistic screening is intended to open a pathway to more comprehensive assessment, an appropriate treatment and support response, and improved health outcomes. Savings are also anticipated in future medical-, social-, and criminal justice-related costs.

Service providers differ in their attitudes and beliefs about decision-making with respect to people seeking help at the clinical/service delivery level. These beliefs reflect agency mandate, training, and personal experience. Some professionals may practice without using formal or validated screening and assessment tools; instead they rely on their training and experience to guide problem identification and client-focused decisions. Some may have philosophical and ethical concerns about asking about mental health and addiction issues, considering it to be intrusive or possibly harmful due to potential stigmatization and labeling (e.g., in educational settings). Some may doubt the increased efficacy and efficiency of these tools over their routine decision-making processes. Some may be reluctant to engage in consistent, structured screening due to concerns that they do not have the expertise or resources to address the concerns identified. Research suggests that critically important mental health and addiction concerns are missed when structured tools and processes to prompt thorough questioning are not used (Zimmerman and Mattia 1999). Research also shows that screening is most effective when combined with other staged investigations and matched therapeutic- and motivation-based interventions (Gilbody et al. 2007). Collaborative approaches can serve to mitigate the reluctance of professionals to use formal screening techniques by bringing together complementary services and resources, ultimately building capacity for improved service to individuals who come to them for assistance.

Given the high level of heterogeneity in demographic, cultural, and clinical characteristics of people needing treatment and support for substance use problems,

it is axiomatic that no approach will meet their needs. This calls for a thorough investigation of needs and strengths and a co-constructed matching of this profile to available service options across a continuum of care. The focus on screening and assessment is intended to increase the efficiency of client intake and engagement, improve individual treatment outcomes, and minimize service delivery costs across the system as a whole (Hilton 2011).

Best practices for treatment and support of people with co-occurring disorders who are already engaged with specialized services also call for more proactive screening of these co-occurring problem areas (Rush and Nadeau 2011). This includes screening for mental health problems among people seeking addiction treatment as well as screening for high-risk/hazardous substance use and addiction-related problems among people seeking mental health treatment and support (Health Canada 2001; Rush and Castel 2011). Proactive, systematic screening can identify a wide range of unidentified problems that may impact treatment engagement and outcome among people with co-occurring disorders (e.g., health risks, suicide ideation, chronic health problems, psychosocial challenges). As noted, the screening process must be followed up with more comprehensive assessment, appropriate interventions, and outcome monitoring. A conceptual framework is presented below to help guide tool selection and service planning across this trajectory. Different screening and assessment tools and processes align with the full spectrum of mental health and addiction-related risks and harms and must "fit" with the varied service delivery settings where people are presenting for assistance.

81.2.2 Collaborative Models for Screening and Assessment

Ideally, screening should occur at the point of first contact with the treatment system, which could be a provider at any level of care, and in one of multiple sectors. As such, it is important that providers across sectors have the knowledge and skill to implement appropriate screening processes and tools that are feasible in their context and useful in identifying the person's needs and determining recommendations for further screening, assessment, treatment, and support. Depending on the results of screening and initial assessment, people need to be connected to the level and type of service most suited to their needs, including health promotion and preventive services. In fragmented systems, where collaboration between services and sectors is not well developed, individuals may not get the services they require in a timely manner, if at all, and systematic screening and assessment may facilitate increased access to services.

Many service providers external to the specialized mental health and addiction treatment sector do not have the expertise and resources to identify mental health, addiction, and co-occurring concerns. Further, most specialist service providers do not have the resources to respond to the breadth of complex issues and problems that are identified through many screening tools. Collaborative care models provide the opportunity for various providers to bring together their collective strengths and capabilities to construct a system whereby individuals are screened and can receive

required services in a seamless manner. Screening processes must be connected to fully articulated *response protocols* in order to be useful and effective. These protocols should describe required actions based on positive results on screening tools, including recommendations for more in-depth screening and assessment and follow-up consultation and referrals. In collaborative models, each provider must be clear about their role in screening and assessment, including the response protocols, so that individuals get what they need from the most appropriate resource. There are various models of collaboration that can incorporate screening, assessment, and referral protocols, and these include:

- *Integrated treatment and support for people with co-occurring disorders*, whereby competencies and processes related to screening and assessment are key criteria for defining integrated programs as "concurrent disorder capable" (McGovern et al. 2010).
- *Single assessment process incorporating multidisciplinary assessment* – Single assessment processes reduce the number of assessments between mental health, addictions, and various health and social service professionals in order to enable a seamless care process. Another option is to use common screening and assessment tools across a network of providers and with electronic sharing of the information and joint care planning.
- *Centralized access point to care* – This approach aims to reduce the number of points of entry of care for users, in some cases to a single access point in order to reduce the number of professionals and organizations prospective clients and their families have to deal with.
- *Screening*, *Brief Intervention*, *and Referral to Treatment* (*SBIRT*) – This approach requires health and social service professionals to use brief screening instruments to identify people at risk of, or experiencing, mental health and/or addiction problems and who then receive brief intervention on treatment on-site or who are proactively linked to specialist providers depending on severity.
- *Addiction specialists in generic settings* involves either assigning/hiring an addiction worker to perform in-house screening and brief assessment or colocating a worker from a specialized addiction services into the nonspecialized setting, for example, an emergency department.

81.2.3 Best Practices for Screening and Assessment

Through a treatment system lens, there are many disciplines and service delivery settings potentially involved in the screening and assessment process. An individual situation may require input from a medical, psychiatric, nursing, psychological, psychosocial rehabilitation, social work, and/or spiritual perspective. A collaborative approach to screening and assessment requires mutual interprofessional respect for the unique contributions that each has to offer to a client-centered approach. The uniqueness of the various perspectives notwithstanding, common principles include:

- A "whole-person perspective" on strengths and needs
- A sensitivity to diversity and related equity issues

- A strong emphasis on creating a welcoming, motivation-based, therapeutic interface
- Adherence to an evidence-based approach

An evidence-based approach encompasses several factors including clinician expertise, exploration of person characteristics and contextual variables using psychometrically sound tools, critical thinking skills, personal and collateral input, and knowledge of evidence-informed interventions (Jordan and Franklin 2011). Screening and assessment must be seen as a *process* that continues over time as more information is shared and therapeutic relationships strengthen. A collaborative, longitudinal approach is particularly critical for the assessment of complex, co-occurring disorders (Kranzler et al. 1994) given the need to disentangle etiological sequencing (e.g., depressive symptoms induced by heavy alcohol use). In a collaborative approach to screening and assessment, the *sharing* of information across service providers is also critical. If possible, this should be done through e-health technology, but minimally through telephone, email, or written communication. Interprofessional communication has been shown to be an effective component of collaborative care (Foy et al. 2010).

Best practice entails a staged approach that links screening, assessment, and outcome monitoring with a family of tools and related decision-making processes that are developmentally appropriate and delivered through a diversity-based approach to ensure equitable access and subsequent assessment and treatment. This approach has been articulated in the *Conceptual Framework for Screening and Assessment* described below (Fig. 81.1). This framework is consistent with the emphasis on staged assessment and interventions in the area of mental health assessment for primary care (e.g., Bufka et al. 2002), addictions assessment generally (Carroll 1995; Donovan 1999; National Treatment Agency 2002; Miller 2006), and co-occurring disorders (Drake et al. 1998). It is also consistent with the evidence from the literature on the screening for depression, namely, that screening is more effective if (a) the priority group for getting feedback has been defined on the basis of a predetermined cutoff for "high risk" rather than universally for the whole population screened (Gilbody et al. 2007) and (b) positive screening results need to be followed by concrete steps to further explore strengths and challenges and provide intervention and supports for ongoing client engagement and transitioning to required services (Gilbody et al. 2003). Importantly, guidelines and supporting evidence for SBIRT with respect to alcohol and/or drug use refer to the *overall system* of screening, brief intervention, and referral, not just the screening component.

The framework can assist in choosing the "right" tools and using them with the "right" people at the "right" time. It is recommended that in order to effectively apply the framework, it be considered in the context of a multi-sectoral continuum of care and the specific collaborative models and service delivery settings under consideration. In the application of the framework in specific community contexts, it may be the case that the required level of care is not readily available due to waiting time or the lack of service availability within the jurisdiction or via realistic distance/travel time. Collaborative arrangements with existing services may be

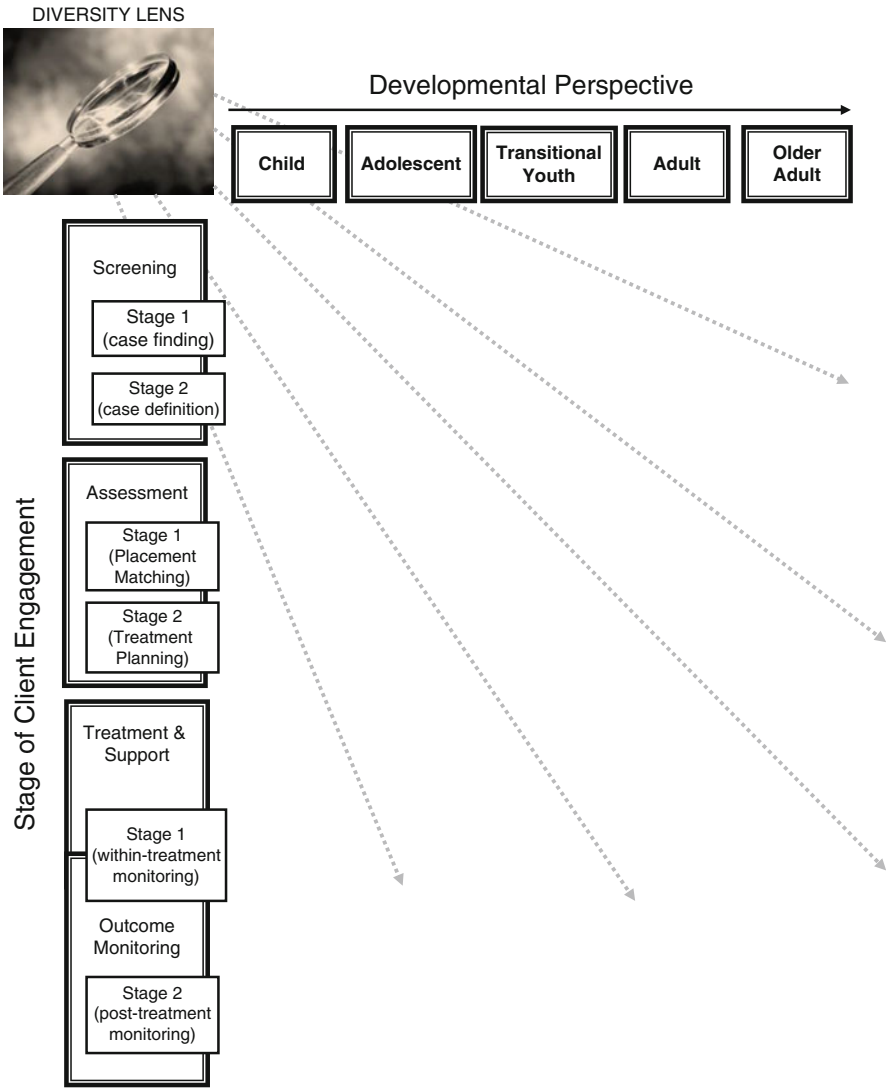

Fig. 81.1 Conceptual framework for screening and assessment in context of collaborative care (Adapted from Rush and Castel (2011))

required in order to offer the best service available at that point in time and to maintain client engagement. Parikh (2008), for example, discusses the types of evidence-based services and supports for mental health problems that can be provided within addiction services following positive results on mental health screening tools. Flynn and Brown (2008) note that, in the case of people with co-occurring disorders, provision of mental health services will often reduce

substance use and ameliorate addiction-related problems. Evidence reviewed by these same authors also suggests the reverse to be true for the provision of addiction treatment and consequent reduction of many mental health-related symptoms and improved functioning.

In short, it is important to work with local resources as best as possible while advocating for additional resources. In rural and remote areas, where resources may be limited, tele-psychiatry may also be an option. Therapist-assisted screening, assessment, and intervention via Internet or mobile-based technology are also an area of high need for more research and development in order to increase service options (see, e.g., Cunningham and Van Mierlo 2009; Andrew et al. 2010; Fjeldsoe et al. 2009).

81.2.3.1 Diversity Lens

Every individual has a unique and complex set of circumstances, perspectives, strengths, and concerns shaped in large part by the social determinants of health and including, for example, gender, sexual orientation, culture, ethnicity, social location, geography, political views, and religious/spiritual affiliation. As such, each component of this framework must be considered through a "diversity lens" when implementing tools, interpreting the results, and providing feedback to individuals in the context of day-to-day service delivery. The diversity lens is also critical when conducting research on screening and assessment tools and processes, for example, working to ensure tools are validated in specific populations and are culturally appropriate.

81.2.3.2 Developmental Perspective

Development stage, an important determinant of health, is a core element of the conceptual framework. The horizontal axis of the framework articulates the developmental trajectory across the lifespan as a frame of reference to also guide the choice of screening and assessment tools and processes. At each stage of this trajectory, there are specific developmental tasks and challenges that an individual must navigate. The diversity lens described above further nuances and elucidates complexity at each life stage. Age cutoffs for each developmental stage may vary for the individual, although most programs and funders allocate services by age rather than stage. Similarly most tools are validated for use with groups of individuals defined by age rather than stage. For example, some transitional age youth in the 18–24 range would be well served by screening and assessment with adult measures and being treated in the adult sector and others, adolescent measures and the youth sector. Therefore, tools and services that can be applied differentially to match developmental stage, rather than being bound by strict age boundaries, are preferred. The GAIN-Short Screener (Dennis et al. 2006) is appropriate for use from age 10 to older adulthood and is, therefore, particularly helpful for collaborative, system-level application (Lucenko et al. 2010).

Developmental stage and consideration of service delivery settings that may be unique to specific stages are also important considerations for determining *when* during the engagement, treatment, and support process to ask different types of

screening questions. For example, for young people being seen on an outreach basis in their school or street environment, it would not be appropriate to begin asking screening questions about sensitive topics such as high-risk sexual behavior, trauma experiences, or illegal behavior before a trusting relationship has been initiated. This will also be the case in many other settings and populations. Interpretation and action in response to screening results also need to be developmentally informed. More attention has been paid to this issue with respect to children, adolescents, and adults, but insufficient attention has been paid to further articulating the role of developmental stages in service transitions for transitional-aged youth and older adults. These developmental stages have been incorporated into the framework to ensure specific consideration is given to individuals in these life stages so that their unique issues and concerns are not overlooked.

81.2.3.3 Stages of Client Engagement

The vertical axis of the conceptual framework describes the stages of engagement that are situated across the continuum of service provision from problem identification or case finding to outcome monitoring. A collaborative approach to screening and assessment can be facilitated by a shared acceptance of this staged approach. As noted above, a staged approach is essential to ensure positive outcome for the individual and to improve the efficiency with which people are engaged in a treatment and support system (Hilton 2011). This staged approach also helps operationalize an "any door is the right door" principle in several treatment system designs. When placed in the context of an integrated screening and assessment *process*, sequentially implemented screening tools work together to ensure progressive but judicious and efficient use of assessment resources to guide the planning of client-centered treatment and support. In addition to screening, there are also two stages of assessment followed by some level of treatment and support and outcome monitoring. Assessment, intervention, and outcome monitoring are all linked to results from initial screening tools at a conceptual and measurement level and ideally through shared information technology. Collectively the resulting information and decision-making processes inform both ongoing treatment and support planning for the individual as well as evaluation and performance measurement at the program and system level.

While the two stages of screening and the two stages of assessment represent a *continuum* of information gathering and decision-making, some helpful distinctions can be made between these groupings nonetheless. It is beyond the scope of this chapter to provide an exhaustive review of the many screening tools that have been developed and tested for work in the substance use area and for application in addictions, mental health, and other settings such as primary care. There are several excellent narrative reviews that cover the large majority of available tools, and it is important to review the relevant literature carefully to assess the available research data on psychometric performance in specific populations (i.e., reliability, validity, sensitivity, specificity, positive and negative predictive power) and factors related to usability such as length, cost, and recommended mode of administration, to name just a few factors. Some of the existing reviews cover tools of particular relevance

to primary care and other health-care settings (e.g., Allen et al. 1995; McPherson and Hersch 2000). Other reviews are more oriented to the area of co-occurring disorders and address the potential applicability of tools for settings such as mental health, addiction services, and criminal justice (Center for Substance Abuse Treatment 2005; Health Canada 2001; Sacks 2008; Savage 2006; Centre for Addiction and Mental Health 2006). Some reviews do not distinguish the settings for application but rather focus on the characteristics of the tools (e.g., Dawe et al. 2002; Tucker et al. 2004). Still others focus on children and youth as opposed to adult populations (Pediatrics 2010; Centre for Addiction and Mental Health 2009; Rush et al. 2009). While there is no shortage of synthesized information about the various options for screening and assessment, it may still be a challenge to sift through the available information as each review often has a particular focus (setting, population, mental health broadly, or addiction specifically).

81.2.3.4 Screening

In the context of addictions, and the broader field mental health, screening is a relatively brief process designed to identify individuals who are at risk of having particular problems or diagnosable disorders that warrant immediate attention, intervention, or more comprehensive review. Identifying the need for further assessment is the primary purpose of screening.

A staged approach to screening involves the sequential use of tools for risk assessment/case finding (Stage 1) and case definition (Stage 2). An important objective of this staged approach is to reserve the tools that require more staff time, resources, and training for those individuals who score above the cutoff on the briefer, more economical tools. The organizational context will dictate whether screening will start at Stage 1 or 2, as further described below.

81.2.3.5 Stage 1 Screening: Risk Assessment/Case Finding

This stage of screening involves the use of psychometrically sound, typically self-report questionnaires that cast a fairly wide net to determine the possibility of a particular problem area or mental/addictive disorder, and which requires further investigation. In the addiction area, Stage 1 tools may also focus on the level of risk associated with alcohol and drug use per se, the AUDIT perhaps being the best known option (Babor et al. 2001).

Having a menu of Stage 1 tools to choose from, ranging from brief 1-3 item instruments to somewhat longer tools that focus on a small number of domains, can facilitate the implementation of systematic screening protocols in emergency rooms, primary care offices, and other service delivery settings where severe time constraints may otherwise preclude a more detailed, systematic screening approach.

Stage 1 tools are characterized by their brevity (typically between 1 and 20 items; completion time less than 5 min) and low-threshold training requirements and scoring algorithms. There have been recent developments toward very brief screeners (1–3 items) for alcohol or other drugs in order to facilitate screening in busy settings such as primary care or emergency departments (e.g., Smith et al. 2010; Ramchand et al. 2009) or with high-need populations that cannot tolerate completion of long

questionnaires (e.g., people with psychosis: Ley et al. 2007). As noted, the AUDIT (Babor et al. 2001) is a Stage 1 tool focused on the level of risk of alcohol consumption. Others are focused on consequences, including substance use/abuse or dependence (e.g., CAGE, Ewing 1984; Dhalla and Kopec 2007; BASIC, Bischof et al. 2007; TWEAK, Russell 1994; and CRAFFT, Knight et al. 1999).

The screening for mental health problems/disorders is also highly relevant for the assessment and treatment of people with identified substance use concerns. With respect to screening for mental health challenges, there is an important distinction between disorder-based tools and those based on a dimensional approach, such as measuring mental distress. Others that are longer such as the Beck Depression Inventory (Beck 1961), the Beck Anxiety Inventory (Beck et al. 1988), or screeners for PTSD (SPAN: Meltzer-Brody et al. 1999) and trauma (Klein et al. 2002) are best considered follow-up Stage 2 tools because of their length and diagnostic specificity. Disorder-based tools that are extremely short, such as those using 1–3 items for identifying depressive and/or anxiety disorder (e.g., the ADD: Means-Christensen et al. 2006), are considered Stage 1 screeners. However, Stage 1 mental health screeners also include brief dimensional measures such as the K6/K10 (Kessler et al. 2002), the five-item mental health component of the SF-36 (Ware and Sherbourne 1992; Berwick et al. 1991); the Psychological Screening Inventory (PSI: Lanyon 2006); and either the Brief Symptom Inventory or the BSRS (Derogatis and Mclisaratos 1983; Lee et al. 2006), both being shorter versions of the Symptom-Checklist 90-R (Derogatis 1983; Benjamin et al. 2006). For children and adolescents, the Strengths and Difficulties Questionnaire serves as a useful Stage 1 mental health screener (Goodman and Goodman 2009).

A small number of Stage 1 screening tools focus on *both* mental health and addictions, and these are highly valued because of their broader coverage and, therefore, their applicability in multiple settings involved in a collaborative care arrangement. The GAIN-SS (Dennis et al. 2006) is one such tool rapidly growing in popularity across North America and now available in multiple languages.

Biological tests for alcohol and drug use may also be helpful and have the advantage of ease of application in medical settings and their utility as a supplement to self-reported information. Limitations include cost, lack of specificity and, in some instances, sensitivity to recent substance use. Biological testing includes alcohol breathalyzer testing, measures of tissue damage from chronic substance use such as reflected in the liver enzyme gamma-glutamyl transferase (GGT) or red blood cell mean corpuscular volume (MCV), and hair, saliva, and urine analysis (see Tucker et al. 2004; Greenfield and Hennessey 2008 for brief reviews).

Time and resources permitting, brief screening across other selected domains is also recommended. Screening for other health problems such as traumatic brain injury, cognitive impairment, fetal alcohol spectrum disorder (FASD), HIV/AIDS, and tobacco use is also of critical importance to treatment and support planning and may be called for in some health-care settings using additional, brief screeners.

81.2.3.6 Stage 2 Screening: Case Definition

This second step in a staged approach to screening involves the use of psychometrically sound tools that are more specific and longer than those used in Stage 1 and which aim to tentatively identify one or more *specific disorders or problem areas*. This may include alcohol or other drug abuse and dependence and other mental disorders such as psychotic disorders, major depressive disorder, a variety of anxiety disorders including PTSD, eating disorders, and ADHD.

Although more specific and detailed than Stage 1 screeners, the information gathered through the tools in this category of the staged approach is still NOT sufficient on which to base a formal diagnosis, although some of the names of the tools can be misleading in this regard. The administration of a Stage 2 screening tool may involve the same or a different service provider than the one undertaking the Stage 1 screening. In any instances involving a transition to a new partner in a collaborative care process, a motivational approach and transition supports to ensure ongoing engagement are critical, especially for people with complex co-occurring conditions.

Screening tools such as the Psychiatric Diagnostic Screening Questionnaire (PDSQ: Zimmerman and Mattia 2001) and the Modified Mini Screen (Alexander et al. 2008) are particularly helpful as diagnosis-based, Stage 2 screeners. Rush et al. (2013) validated the PDSQ, as well as the psychiatric subscale of the widely used Addiction Severity Index for identifying mental disorders among people seeking addiction treatment. Magruder et al. (2005) found both the PDSQ and the Conners' Adult ADHD Rating Scale also performed well in adult substance use treatment settings. For adolescents, the POSIT (Danseco and Marques 2002) is more focused on specific problem areas rather than diagnosis (e.g., substance use, health, school, family) and is a well-validated option for Stage 2 screening in several settings. Others for children and youth are the Child Behavior Checklist (CBCL: Achenbach 1991) and the DISC-R (Lucas et al. 2001) although it covers most mental disorders and substance use. For more discussion on specific screening tools and processes for children and youth, see the narrative review conducted by Rush and colleagues (2009) and synthesized by the Centre for Addiction and Mental Health (2006). As noted earlier tools such as the Beck Depression Inventory (Beck 1961) and the Beck Anxiety Inventory (Beck et al. 1988) are considered to be Stage 2 tools due to their specificity in terms of diagnosis and length. This grouping also includes several mental health screening tools that are dimensional rather than diagnostic in nature such as the longer version of the GHQ-30 and the full SCL-90-R (Derogatis 1983).

81.2.4 Assessment

In the staged framework, assessment is also conceptualized as involving two phases. Stage 1 assessment is focused primarily on further information gathering and placement/referral to the most appropriate service setting (i.e., level of care). This needs to occur within a stepped-care, integrated systems model that provides

supported transitions across levels of care on an as-needed basis, including multiple sectors of services. Upon engagement in the appropriate setting, Stage 2 assessment goes further in examining strengths and needs across several bio-psycho-social-spiritual domains including health and mental health status, family/social situation, environmental risk factors, etc. One helpful way to conceptualize the distinction between Stage 1 and Stage 2 assessment is that between "placement" and "modality" matching (Mee-Lee and Gastfriend 2008; Gastfriend et al. 2000). Placement matching refers to initial client assignment to a treatment setting with a certain resource intensity and, therefore, important cost implications. Modality matching refers to client assignment on the basis of the optimal clinical approach and intervention(s), including philosophical and goal orientation such as reduced substance use versus abstinence, based on the full profile of client strengths and needs.

The two stages of assessment are further described below.

81.2.4.1 Stage 1 Assessment: Information Gathering and Service Placement

This first step in a comprehensive assessment involves continued information gathering that is optimally done through use of valid tools and structured interviews. There is a gray area between Stage 2 screening and Stage 1 assessment, this being a matter of degree in the level of detail and duration of time for information gathering, case construction, and the initial development of treatment and support plans. However, the essential feature of a Stage 1 assessment, especially in the context of collaborative care across multiple service delivery settings, is the intention to efficiently gather enough information on both strengths and needs, including immediate needs for physical and psychosocial stabilization, to formulate an initial placement/referral in an appropriate level of care.

For addiction services, this would include a determination of the need for withdrawal management which may be initiated in one of the three levels of care: home/mobile, community/medical, or, in the case of complex co-occurring mental and physical problems, a hospital-based service with adequate medical and psychiatric supports. The CWAW-Ar is an assessment tool that supports determination of the need for withdrawal management services (Sullivan et al. 1989). Withdrawal management often needs to be accompanied by a period of stabilization prior to formal engagement in treatment. Aside from withdrawal management, a Stage 1 addictions assessment should also determine the need for community or residential treatment at varying levels of duration and intensity. These levels of care are articulated in considerable detail in the ASAM criteria for placement/referral to addiction services (Gastfriend 2003; Mee-Lee and Gastfriend 2003).

It is critical to reemphasize that the initial placement/referral based on the Stage 1 assessment be undertaken in the context of a stepped care, potentially multiservice model – that is stepping up to a higher level of care if required and stepping down on the basis of progress toward the individual's goals. At moderate-to-high levels of severity and case complexity, this typically requires transition support, including case management and shared e-health information. It also requires monitoring of outcomes, within and posttreatment (see below).

The ASAM model specifies the dimensions across which a clinician must explore strengths and needs in order to make the appropriate placement match (Gastfriend and Mee-Lee 2003). These dimensions include:

- Acute intoxication and/or withdrawal potential
- Biomedical conditions and complications
- Emotional, behavioral, or cognitive conditions and complications
- Readiness to change
- Relapse, continued use of continued problem potential
- Recovery environment

It is highly recommended that these areas be examined with a semi-structured or a structured interview approach facilitated by validated instruments that support the initial placement/referral.

Assessment tools and processes for Stage 1 assessment include the GAIN-Q3 Standard MI or the GAIN-I-Lite – these tools being part of the GAIN "family" of substance abuse screening and assessment tools (www.chestnut.org). As with the GAIN-SS, these brief assessment tools are appropriate for use with individuals from age 10 and up. Another instrument for Stage 1 assessment is the Recovery Attitude and Treatment Evaluation (RAATE: Gastfriend et al. 1995; Mee-Lee 1988; Najavits et al. 1997).

81.2.4.2 Stage 2 Assessment: Case Conceptualization/Comprehensive Treatment Plan

The next stage of the assessment process involves the creation of a case conceptualization, formulation, and/or diagnosis leading to an individualized and adaptable treatment plan. The language around this overall process changes depending on the discipline and service delivery setting. The central idea, however, is to pull together all the information that has been gathered from validated screening tools, undertake additional information gathering as needed through assessment questionnaires, structured and semi-structured interviews, collateral contacts, and case notes from previous service contacts (if available). The resulting case conceptualization or diagnosis informs the treatment plan, including responding to instrumental and clinical needs and providing indicated referrals. The term "modality matching" summarizes the intention of a Stage 2 assessment, although this may also involve revision to the placement decision made at an early stage.

Increasingly, Stage 2 assessment is seen as being grounded in the present context of the person's life situation and problem focused (Jordan and Franklin 2011). This approach, however, should not exclude consideration of critical underlying factors such as trauma, including intergenerational trauma, and neuropsychological mechanisms. A thorough health assessment including a full psychiatric assessment may also be required and is especially indicated for individuals presenting with more complex co-occurring conditions.

It is beyond the scope of this report to delve into all the critical issues involved in the person-clinician interface for purposes of comprehensive assessment and treatment and support planning. There are many excellent reference texts that approach this from various disciplinary perspectives, including psychiatry

(First and Tasman 2006; Greenfield and Hennessy 2008), psychology/behavioral health (Miller 2006; Tucker et al. 2004), or social work (Jordan and Franklin 2011). All such experts acknowledge the role of clinician experience and skills in conducting semi-structured or structured interviews that operationalize core principles and practices such as sensitivity to individual differences in culture, diversity, and developmental age; the need for empathy and establishing therapeutic alliance; and the appropriate involvement of family and significant others. In the addiction field, there is a need for such interviews to cover several areas including, but not limited to, substance use history, including age of first use and onset of negative consequences; severity of substance abuse/dependence; level of insight into past and current challenges; social supports and environment risk factors (e.g., for relapse); medical and psychiatric comorbidity; current phase of use (e.g., intoxicated or in withdrawal); and pressures to seek help and the person's readiness/motivation for change. For many of these areas, the approach is to explore these areas at a deeper level than they have been investigated in Stage 1.

In the addictions field, there have been significant efforts to create integrated assessment packages to support individualized treatment plans and subsequent follow-up determination of outcome. Two well-known comprehensive addiction assessment packages are the Addiction Severity Index (McLellan et al. 1992; version 6) and the GAIN-I (www.chestnut.org). The GAIN-I is now used extensively in North America and has the added advantage of being conceptually and instrumentally linked to the GAIN-SS (Stage 1 screener) and the GAIN-Q3 or GAIN-I-Lite (Stage 1 assessment). Another example with a stronger focus on mental health is the Psychiatric Research Interview for Substance and Mental Disorders (PRISM) which, although designed primarily as a research tool, provides systematic coverage of alcohol/drugs and mental health experiences and symptoms and functional impairment (Hasin et al. 1996). There is also the option to administer the full structured interview for DSM-IV disorders (DSM-IV) (First et al. 1996) although this would need to be supplemented with other addiction specific tools assessing, for example, readiness to change.

81.2.5 Treatment and Support and Outcome Monitoring

These stages of the staged framework will only be briefly summarized as they are somewhat out of the scope of the present focus on screening and assessment. Outcome monitoring is, however, critically tied to these earlier stages because of the need to establish baseline status early in the treatment process and to inform and engage the client in the eventual follow-up processes, for example, obtaining locator information. Importantly, a connection is now made between *within-treatment outcome monitoring* and *posttreatment* outcome monitoring with recovery checkups. Importantly, both within-treatment monitoring and posttreatment outcome monitoring consider the contact for client and program evaluation purposes, an extension of the treatment and support process itself. This is conceptually quite different than a traditional "research" follow-up and much

more likely to engage administrative and clinical staff, as well as clients themselves, in the outcome monitoring process.

81.2.5.1 Stage 1. Within-Treatment Monitoring

Within-treatment outcome monitoring tracks progress on an ongoing basis with very brief but highly relevant clinical tools applied at the front end of periodic therapist-client interactions. This model has evolved from the work of Lambert in the mental health area (e.g., Lambert et al. 1996) and, in the addiction field, McLellan and colleagues (2000). This stage of outcome monitoring occurs at the clinical interface of therapist and client. It is critical that the outcome measures be brief, be implemented within the flow of the clinical encounter, and return feedback immediately in a useful format to further the therapeutic relationship and the client's progress toward goals. Appropriate within-treatment outcome monitoring can be accomplished with repeat application of some screening tools that are sensitive to change over time such as the GAIN-SS. Others such as Lambert et al. (1996) Outcome Questionnaire (OQ) have been designed specifically to assess psychological processes that cut across many types of mental health problems, including addictions.

81.2.5.2 Stage 2. Posttreatment Monitoring

Posttreatment outcome monitoring involves the repetition of selected screening/assessment measures at some interval after program admission, such as 3,6,12, or 24 months, and determination of changes in these measures. In addition, the follow-up contact is an opportunity to re-engage the individual in treatment if indicated, using a guided, motivational return-to-treatment protocol (Dennis et al. 2003; Scott and Dennis 2009). Posttreatment monitoring is useful as an accountability and program evaluation tool and can also be helpful in identifying clients who may be struggling and need further assistance to recoup gains made in treatment.

Ideally, posttreatment follow-up also involves repeat application of one or more assessment tools or sub-scales by phone or face-to-face interview. The GAIN-I and GAIN-Q3-standard (www.chestnut.org) on the Addiction Severity Index (McLellan et al. 1992) are useful measures for outcome monitoring. Locating clients and obtaining good follow-up rates (ideally over 80 %) are the Achilles' heel of posttreatment follow-up for addictions programs. There are protocols for achieving substantially higher follow-up rates (Scott 2004), and these can benefit from collaborative networks working together to locate and engage people in the follow-up process.

81.2.6 Is Screening for Mental Health and Addictions Effective?

The usual approach to answering this question about the effectiveness of screening is to assess whether the screening tool(s) and related process are successful in identifying people with mental health and/addiction problems that would not have been identified through routine care. Although this has rarely been put to the test in

a systematic way (see Gilbody et al. 2007 for a synthesis of the research in the area of depression), the well-documented level of undetected problems combined with the high predictive value of many validated screening tools points to the importance of systematic screening to improve case detection.

There are, however, two additional aspects to the effectiveness question. The first is to ask whether the screening tools and processes, and subsequent review of the results, contribute to the management of the index problem. In other words, does it lead to meaningful action on the part of clinicians that would otherwise not have occurred? Secondly, one must ask if, at the end of the day, the screening and subsequent action have improved the index problem or related challenges. The systematic review on screening for depression by Gilbody et al. (2007) suggests that screening can contribute to better care management and health outcomes if there is some selectivity in providing feedback to only moderate-to-high-risk cases, rather than all people who may score positive according to test guidelines. This highlights the fact that screening *alone* may make little difference without a detailed response plan and follow-up intervention. In the addiction area, there is ample evidence that screening for different levels of risk for alcohol and drug use, accompanied by brief intervention or referral to treatment, is effective in engaging people in both these response options and subsequent outcomes (Babor et al. 2007; Madras et al. 2009; Kaner et al. 2009). More research is needed, however, to tease out the most effective ingredients of the overall SBIRT protocol. More work is also needed on addressing the challenges implementing SBIRT protocols in health care and other settings (Johnson et al. 2010; Williams et al. 2011).

The context in which screening takes place must be carefully considered in both implementation and evaluation of screening and assessment tools and processes. As already mentioned, the role and purpose of screening should be well understood and articulated in the context of the mandate and objectives of the service provider. Organizational policy must also support the implementation of screening and related protocols. Required staff competencies and program design should fit within clear service delivery protocols addressing where, when, and how screening will be administered and how the information gathered will be used. Personnel who are administering the tools must be trained to introduce, administer, score, discuss, and take appropriate action based on the screening results. All of this needs to be clearly conveyed to individuals engaging with the service so that they understand how screening can be helpful and provides fruitful ground for evaluative inquiry.

As noted above, implementing formal screening tools and processes is a logical fit in the specialized substance abuse treatment sector. In these settings, clients have already been identified as needing further screening, assessment, or treatment, and consideration needs to be given to screening for co-occurring concerns beyond the initial presenting problem, such as mental health. In other settings where routine screening and assessment of various health concerns is already taking place (i.e., primary care), the rationale for extending screening to identify addiction problems is also clear. Screening in settings such as schools, employment counseling, and justice settings is important to consider given the evidence that rates of addiction and mental health problems are high and often not identified. While these

settings provide important opportunities for early identification and early intervention, there are a number of potential risks that must be considered, including stigma resulting from identification and labeling, social exclusion, limitation of opportunities, and false-positives consuming scarce treatment resources. Risks associated with identification may be greater for specific individuals, for example, severe sanctions may be imposed on those identified as being involved in substance using activities by some schools, employment programs, shelter and housing providers, residential services in the mental health sector, long-term care facilities, families, and specific ethno-cultural groups and communities.

Models of collaboration within which screening and assessment are core activities provide the field with rich evaluation opportunities, including outcome and process evaluation and an opportunity to monitor trends and performance. Outcomes can be examined at the individual (i.e., client and service provider), organizational, and community level. For example, at the organizational level, outcome indicators could include changes in staff attitudes, skills, and behavioral engagement in screening and assessment practices and change in referral practices as well as client perceptions of care; at the community level, indicators could include increased numbers of new clients referred to treatment and reduced number of emergency visits. It is also of interest to evaluate the extent to which the development of collaborative models of screening and assessment contribute to collaborative processes across agencies/service providers – for example, increased partnership and building of partnership capital to engage in other joint planning and service delivery. Using a consistent screening tool across a collaborative group of service providers provides an opportunity for decision-makers, funders, and researchers to look at presenting needs across settings and monitor trends over time within the collaborative as well as in comparison to the general population (Henderson and Chaim 2013).

81.3 Conclusion

There is a very strong rationale for a more proactive concerted effort to screen for mental health problems and at-risk consumption of alcohol and other drugs and related addictions problems given the evidence concerning the level of under-detection in routine practice and the performance of a host of screening tools and processes. Screening in multiple sectors, along with follow-up assessment and intervention, is one strategy to broaden the base for attending to addiction-related concerns and increasing the scope and reach of treatment and support beyond the traditional sector of specialized addiction services. There are many reasons to engage in more proactive screening, and both individual and collaborating partners need to be clear about how the information will be used, including making improvements at the system level. When used for clinical decision-making, best practice calls for a staged approach to maximize efficiency of the overall screening and assessment process. The specific tools and processes must be tailored to the setting and target population for which they are being implemented. For example, some tools will work best for screening in primary care and other generic health and

social service settings, and others are more appropriate for screening in specialized mental health and addiction settings. That said, whether working in generic settings such as primary care or specialized settings, a collaborative approach, drawing upon multidisciplinary, multi-provider, and multi-sectoral expertise, is needed across the stages of screening and assessment, along with a collaborative response protocol for level-of-care placement/referral for treatment and support.

The evidence is quite strong with respect to the ability of screening tools and processes to identify individuals needing brief intervention or other treatment and support. This evidence underlies the best practice guidelines that call for targeted screening in generic settings such as primary care and universal screening for all clients engaged with specialized mental health and addiction services. However, the effectiveness literature tells us that screening is only one part of the process of engagement and the results are more equivocal in terms of the impact of the screening per se on subsequent case management and health outcomes, the literature on SBIRT in the addiction field being an important exception. Collectively, the literature that cuts across the mental health and addictions area reminds us that screening alone is unlikely to translate into improved outcomes without a concerted response. Collaborative care processes are likely to contribute to this response, and more research is needed to find the active ingredients of collaborative screening, assessment, and treatment and support processes. Much more research is also needed on the facilitators and barriers to implementing universal or targeted screening and assessment tools and processes at both the level of the individual service provider and within collaborative, shared care arrangements.

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Stepped Care Models in Addiction Treatment

82

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Contents

Abstract

Stepped care models aim at matching treatment intensity to defined patient characteristics in a systematic way, thereby avoiding misplacements and making best use of available treatment resources at the same time. In principle, treatment planning for new patients starts with the least intensive care, progressing to more intensive regimes for nonresponders. Such models have been introduced in psychiatry and in other medical fields.

Models of stepwise patient placement in addiction treatment are known from Northern America (Sobell model, model of the American Society of Addiction Medicine, ASAM) for adults and adolescents and special models for dual-diagnosis patients. Another model comes from Europe (the Dutch model for triage and evaluation in addiction treatment MATE; special model for judicial patients). The various elements and procedures of the ASAM and MATE models are described and compared.

An overview on evaluation studies and reviews is presented, concerning feasibility, validity, reliability, effectiveness, and cost-effectiveness of stepped

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care models. Outcomes are partly positive, but limitations are mentioned and more research is asked for.

82.1 Introduction

82.1.1 A Concept for Patient Placement

It is normal practice to assign a new patient to an appropriate and readily available treatment and to switch a patient not responding to that treatment to another one, be it another intervention type, another medication, or another setting. The therapist makes his or her choice on the basis of guideline recommendations, scientific studies, or personal experience, eventually also on the basis of patient preference.

The concept of stepped care combines a systematized version of such practice with an attempt at matching treatment intensity to patient characteristics. Screening the new patient for specific characteristics provides the basis for treatment indication and placement, starting with the least intensive intervention and stepping up intensity for nonresponders.

Main principle: Patients should be offered the least intensive and intrusive care at first contact, except in case of emergencies and defined complications which ask for an intensive treatment. Otherwise, only nonresponders should receive care along a scale of increased intensity. This principle is aiming to protect patients from intrusive care they do not need and to make best use of available treatment resources by avoiding misplacements. "Stepped care models represent attempts to maximise the effectiveness and efficiency of decisions about allocation of resources in therapy" (Haaga 2000).

82.1.2 Models of Stepped Care

Approaches to stepped care in addiction treatment have been described repeatedly (Mee-Lee and Gastfriend 2008). By now, stepped care models have been introduced in some fields of psychiatry. Guidelines of the National Institute for Clinical Excellence NICE provide stepped care models in the UK for the treatment of depression and anxiety (Richards et al. 2012). In the USA, such resource allocation issues are mentioned for anxiety disorder, panic disorder, eating disorder, and alcohol dependence (Haaga 2000).

82.1.2.1 From First Line to Intensive Care

In the model proposed by the Sobells (Breslin et al. 1999; Sobell and Sobell 2000), the recommended treatment should start with the least restrictive intervention in terms of cost and personal inconvenience for patients. The first step might even involve facilitating "natural recovery" outside of professional services. Stepping up

requires a decision about patient progress and depends on the type of disorder and the effectiveness of available treatments. The decisions may be made on the basis of guidelines, but should not disregard the risk of inappropriate stepping up and of missed stepping up and should include considerations about costs of treatments at different levels.

82.1.2.2 The ASAM Patient Placement Model

The American Society of Addiction Medicine (ASAM) started to develop the patient placement criteria PPC in 1991, and in 1994 the National Institute of Drug Abuse (NIDA) funded a validity study. Revised versions were published in 1996 (ASAM PPC-2) and in 2001 (ASAM PPC-2R). A further revision will be based on DSM-5 to come.

The basis of the model is a concept of individualized treatment: assessment at intake is made in a range of biopsychosocial dimensions (multiaxial DSM diagnoses); assessment dimensions include also readiness to change, continued problem potential, and recovery environment. This is followed by an identification of priority problems, leading to defining the appropriate model and level of service. Progress assessment is used as a basis for eventual reassignment (Mee-Lee 2001; Mee-Lee and Gastfriend 2008; Mee-Lee and Shulman 2009).

Placement criteria have been set up for adults and for adolescents. Special attention is also paid to co-occurring mental and substance-related disorders, in patient assessment as well as in the specifications of services (Mee-Lee 2006). For dual-diagnosis patient, separate risk dimensions are set up: dangerousness/lethality, interference with addiction recovery efforts, social functioning, ability for self-care, and course of illness.

The criteria also advocate for an adequate availability of treatment; by incorporating more use of outpatient care – especially for those in early stages of motivation for change – the criteria help to reduce waiting lists for residential treatment (Mee-Lee and Shulman 2009).

A supplement was published to delineate specific criteria for the use of pharmacotherapies for alcohol use disorders, for detoxification, and relapse (Fishman 2010).

82.1.2.3 MATE: A Model for Patient Assessment and Referral

The Dutch model for measurement in the addictions for triage and evaluation MATE (Schippers and Broekman 2007; Schippers et al. 2010) is a national project, aiming at constructing and testing of a new instrument for the assessment at intake of all problems and needs in relevant domains in substance abuse treatment; the instrument should also be useful as a framework for the application of existing instruments in selected domains for matching, patient allocation, and treatment evaluation in the addictions. The instrument should help to make rational and transparent decisions about providing which and how much treatment to which patients. It was tested for feasibility, reliability, and validity in a population of heavy users, and in a subproject an instrument was developed and tested for judicial clients.

The assessment of substance use disorders at intake is made on the basis of the international classification systems ICD/DSM. Assessment of personal and social

functioning is made in order to determine which type of services will be needed; this part of the new instrument is based on the WHO international classification system of functioning, disability, and health ICF. Existing instruments are used for the assessment of comorbidities, new modules for treatment history, motivation, and criminality. Overall, the MATE instrument is composed of ten modules. A manual and a protocol with detailed instructions were published in Dutch. A German version of the instrument was tested and implemented (Buchholz et al. 2009).

82.1.3 The Main Elements of Stepped Care Models: A Comparative Overview

Stepped care models use three essential elements: patient indicators used for determining the appropriate level of care, treatment typology in regard to intensity of care, assessment, and referral procedures. The following figures summarize the relevant information on these elements in the ASAM and MATE models (Tables 82.1 and 82.2; Figs. 82.1 and 82.2).

82.1.4 Evaluation Results and Perspectives

A systematic review was made on the efficacy of stepped care models involving different levels of psychosocial treatment for alcohol use disorders and nicotine dependence, with or without medication (Jaehne et al. 2012). Little evidence was found to suggest that stepping up nonresponders to more intensive therapy improved outcomes. In one study, the application of a stepped care approach was found to reduce treatment costs compared with usual care. There was some evidence that the greater differentiation between the intensity of the interventions offered at each step, the better the outcome. Further research is needed to evaluate the efficacy of stepped care approaches to providing psychosocial treatment.

Table 82.1 Patient characteristics used for determining appropriate level of care

ASAM assessment dimensions	MATE patient indicators
Acute intoxication and/or withdrawal potential	Addiction severity
Biomedical conditions and complications	Psychiatric impairment
Emotional, behavioural, cognitive conditions/complications	Social stability
Readiness to change	Treatment history 0–1
Relapse/continued use, continued problem potential	Treatment history 2
Recovery environment	Treatment history 3–5
	Treatment history >5

Source for ASAM: Mee-Lee and Shulman (2009), Table 27.1. Source for MATE: Schippers and Broekman (2007)

Table 82.2 Treatment typology

ASAM levels of care	MATE levels of care
0.5. early intervention	1. short outpatient
I. outpatient treatment	2. outpatient
II.1. intensive outpatient	3. day care/residential
II.5. partial hospitalisation	4. care (in- and outpatient)
III.1. low intensity residential treatment	
III.3. medium intensity residential treatment	
III.5. medium/high intensity residential treatment	
III.7. medically monitored intensive inpatient	
IV. medically managed intensive inpatient	
OMT. Opioid Maintenance Therapy	
Levels of care for adult detoxification	
I-D. ambulatory detoxification without extended onsite monitoring	
II-D. ambulatory detoxification with extended onsite monitoring	
II 2-D. Clinically managed residential detoxification	
III 7-D. Medically monitored inpatient detoxification	
IV-D. Medically managed inpatient detoxification	

Source for ASAM: Mee-Lee and Shulman (2009), Table 27.2. Source for MATE: Schippers and Broekman (2007)

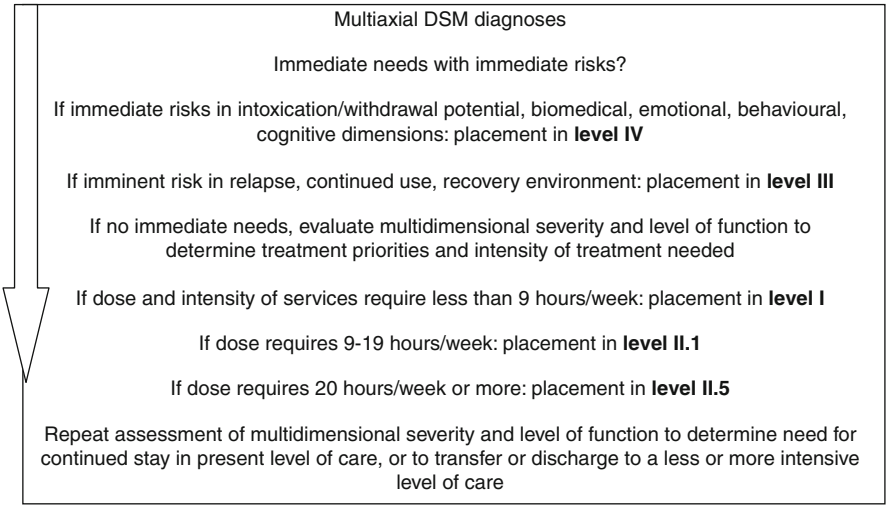

Fig. 82.1 Assessment and referral procedures in ASAM PPC-2r (Source: Mee-Lee and Gastfriend 2008, Fig. 6-1)

Another systematic review of stepped care in psychological interventions was made (Bower and Gilbody 2005). It identified the underlying assumptions on which the benefits of stepped care depend: equivalence in terms of clinical outcomes, efficiency in terms of resource use and costs, and acceptability of "minimal

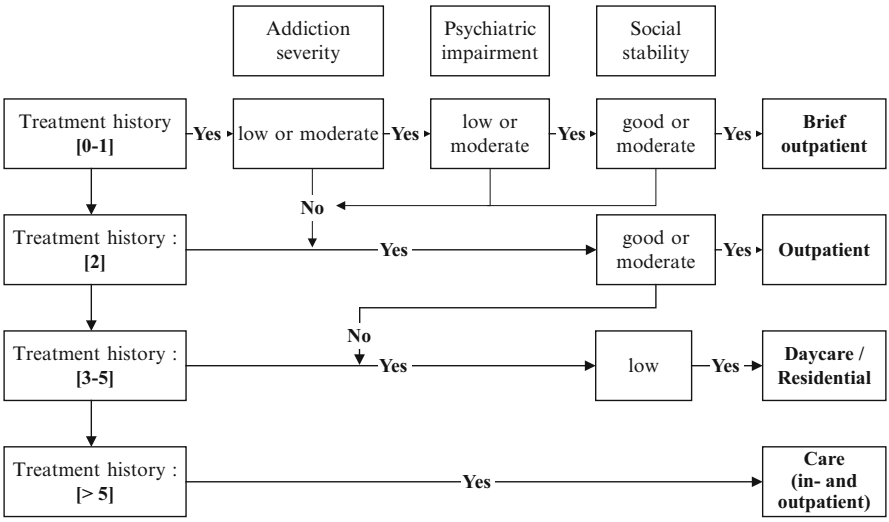

Fig. 82.2 MATE guidance for matching and referral (Source: Merkx et al. 2007, Fig. 2)

interventions" to patients and therapists. The review concludes that more research is needed in terms of rigorous evaluations of the underlying assumptions.

A summary of research on the ASAM patient placement criteria is presented in the Textbook of Substance Abuse Treatment. The authors conclude as follows: "More than a decade of research of the ASAM PPC supports the predictive validity and the cost-effectiveness of the use of PPC. Based on this research, a variety of computer assisted assessment and placement tools are in development" (Mee-Lee and Gastfriend 2008, p. 88). Another overview is presented in the Principles of Addiction Medicine. Nine evaluation studies were performed involving 3,641 subjects; controlled studies found that "treatment based on the ASAM PPC are associated with less morbidity, better client functioning, and more efficient service utilization than mismatched treatment" (Mee-Lee and Shulman 2009, p. 398).

Feasibility and field testing of the MATE in a treatment seeking population was performed in two large treatment settings. Construct validation with related instruments and evaluation of the dimensional structure of modules were performed. Among the results are a satisfactory inter-rater reliability and concurrent validity, indicating the usefulness of the instrument for allocating patients to substance abuse treatment, even in a heterogeneous population (Schippers et al. 2010). However, there were some problems with clinicians not complying with the guidelines, resulting in mismatched patients usually allocated to outpatient treatment instead of early interventions (Merkx et al. 2007).

A comparison of minimal interventions with a stepped care model for patients with alcohol use disorders in the UK evidenced greater cost savings, greater motivation for change, and greater reduction of alcohol consumption for stepped care 6 months after randomization (Drummond et al. 2009).

Further developments: Stepped care models have a considerable potential to improve patient-service matching with improved outcomes and improved use of treatment resources. Stepped care is also considered to be an important element of individualized treatment (Kranzler and McKay 2012). A wider implementation of existing or new models however is slow and may meet problems if not politically supported.

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Harm Reduction Interventions

83

Dagmar Hedrich and Richard Hartnoll

Contents

Abstract

The goal of harm reduction is to reduce both the individual and societal harms of drug use through knowledge-based interventions that change risk behaviors and risk settings. ▶ Chapter 84, "Harm Reduction Policies, Settings, and Challenges" in this textbook gives an overview of harm reduction as a public health policy. This chapter describes the main harm reduction interventions implemented in many countries around the world, synthesizes evidence on their effectiveness and risks, and summarizes key lessons learned. The focus is on illegal drugs, especially opioids and central nervous system stimulants. The interventions covered are opioid substitution treatment; needle and syringe programs; supervised drug consumption facilities; drug overdose prevention; outreach, peer education, and health promotion; testing, vaccination, and treatment

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of drug-related infectious diseases; interventions for stimulant users; and drug-related sexual risk reduction. Key themes stressed include the following: that harm reduction does not replace the need for treatment but adds to the capacity to respond effectively to the wide range of health and social challenges raised by drug use; that the scientific evidence shows that harm reduction interventions are effective in terms of their stated goals, as long as they are implemented appropriately within their contextual settings; and that single interventions are far more effective when implemented together as part of a broader public health policy, including steps to facilitate healthier living and safer social environments.

83.1 Introduction

The goal of harm reduction is to reduce individual and societal harms of drug use through knowledge-based interventions that change risk behaviors and risk settings. ▶ Chapter 84, "Harm Reduction Policies, Settings, and Challenges" in this textbook gives an overview of harm reduction as a public health policy. This chapter describes the major harm reduction interventions, synthesizes evidence on their effectiveness, and summarizes key lessons learned. The interventions covered are:

- Opioid substitution treatment
- Needle and syringe programs
- Supervised drug consumption facilities
- Overdose prevention interventions
- Outreach, peer education, and health promotion
- Testing, vaccination, and treatment of infectious diseases
- Interventions for stimulant use
- Drug-related sexual risk reduction

This overview draws on a wide range of sources from research and practice. Scientific reviews of experimental studies are valuable for assessing outcomes of single, well-defined interventions. However, they are insufficient regarding multidimensional interventions as implemented in diverse, real-life settings. Experimental designs are not always appropriate, feasible, or ethical and are limited to single types of intervention, thus excluding multiple interventions. Often, it is necessary to draw on a wider body of descriptive studies to obtain a fuller picture. Furthermore, it is essential to understand not only outcomes but also how interventions work (process) and how settings influence outcomes. Clinical, sociological, qualitative, modelling, and ecological studies can provide important evidence not only on the impact of interventions and policies but also on "what works and under what conditions."

The focus is on illegal drugs, especially opioids and central nervous system stimulants. Harm reduction approaches have been applied to other drugs including

alcohol, cannabis, and tobacco and to other user groups such as young recreational drug users (Ritter and Cameron 2006; Rhodes and Hedrich 2010).

83.2 Interventions

83.2.1 Opioid Substitution Treatment

Other chapters in this textbook deal with opioid substitution treatment (OST) as a treatment for heroin dependence. Here, the emphasis is on the role of OST in reducing individual and social harms associated with illicit opioid use. Methadone is the main drug employed, though buprenorphine has become more common since the end of the 1990s. In some European countries, heroin-assisted treatment is provided to long-term refractory heroin-dependent individuals who have not responded well on methadone programs (Strang et al. 2012). OST is usually provided in combination with psychosocial treatment, counselling, and other health and social services.

Within a harm reduction paradigm, OST consists of the (usually long-term) prescription of opioid agonists to prevent withdrawal symptoms and craving, thus enabling users to lead more stable lives and to reduce illicit heroin use, risk behavior, and criminal activity. Apart from reduced illicit heroin use, which has been demonstrated in numerous studies (see ▶ Chap. 28 "Opioid Addiction: Short- and Long-Acting Opioids" in this textbook), specific harm reduction outcomes that are sought include reductions in prevalence and frequency of drug injecting and sharing of drug using paraphernalia, incidence and prevalence of infectious diseases (especially HIV and hepatitis C), rates of drug-related mortality (especially overdoses), and rates of drug-related crime. Reductions in high-risk sexual behaviors, as well as improvements in health status, quality of life, and social functioning, are also objectives, though these are not specific to OST.

83.2.1.1 Evidence on Effectiveness

Three major reviews of multiple studies with robust designs all found strong evidence that OST is effective in reducing self-reported prevalence and frequency of injecting, sharing of injecting equipment, and injecting risk behavior scores (Sorensen and Copeland 2000; Tilson et al. 2006; Gowing et al. 2011). The same reviews found clear, consistent evidence that OST in community settings is effective in reducing HIV transmission, especially among those in continuous treatment and when dosages are adequate. A further review estimated that OST is associated with a 54 % reduction in risk of HIV infection among people who inject drugs (MacArthur et al. 2012).

The effectiveness of OST in reducing HCV transmission has been harder to determine because HCV is more easily transmitted through injecting risk behaviors and because baseline prevalence levels of HCV in drug-injecting populations are

often high. While some reviews report little impact of OST as a single intervention (Wright and Tompkins 2006), other recent studies, including a meta-analysis of UK-based studies and cohort studies of hepatitis C incidence among OST clients, suggest a positive impact of OST on preventing HCV infections (Turner et al. 2011; Kimber et al. 2010; ECDC and EMCDDA 2011). There is stronger evidence that OST combined with NSP for clients who continue drug injecting can be highly effective in reducing hepatitis C incidence, if coverage of both interventions is high (van den Berg et al. 2007; Des Jarlais et al. 2010; Turner et al. 2011).

There is strong, review-level evidence that OST reduces substantially the risk of overdose mortality, as long as doses are sufficient and continuity of treatment is maintained (Amato et al. 2005; Caplehorn et al. 1996; Kimber et al. 2010). A systematic review and meta-analysis of mortality among regular or dependent users of heroin from 58 prospective cohort studies, mostly of OST, found that treatment is clearly protective against mortality (Degenhardt et al. 2011).

There is clear, consistent evidence from many studies that criminal activity, arrest, and incarceration rates decline markedly after patients enter OST and that this effect is stronger the longer they remain in treatment (NIDA 2006). This is particularly true of drug-related criminal activity such as drug-dealing and acquisitive crime. Where sufficient coverage of opioid using populations is achieved, decreases in drug-related crime at individual level are reflected in reduced levels of crime at community level.

A recent systematic review of 21 studies conducted in prison settings concluded that the benefits of OST provided in prison are similar to those obtained in community settings (Hedrich et al. 2012). OST was significantly associated with reduced heroin use, injecting, and syringe sharing in prison if doses were adequate. Prerelease OST was significantly associated with increased treatment entry and retention after release if arrangements existed to continue treatment. For other outcomes, associations with prerelease OST were weaker. While some post-release reductions in heroin use were observed, evidence regarding crime and re-incarceration was equivocal. Due to lack of studies, there was insufficient evidence concerning HIV/HCV incidence, either in prison or post-release. There was limited evidence that prerelease OST reduces post-release mortality. Disruption of OST continuity, especially due to brief periods of imprisonment, was associated with very significant increases in HCV incidence (Dolan et al. 2005). There is also evidence that OST facilitates improved adherence to HIV treatment (Palepu et al. 2006) and modest reductions in high-risk sexual behaviors (Gowing et al. 2004; CDC 2012a).

83.2.1.2 Conclusion

Benefits of OST that have been clearly established include reduced illicit heroin use, injecting and risk behaviors, reduced HIV incidence, overdose mortality, and criminal activity. Reductions in HCV incidence, though reported in some studies, are less well established.

In prison settings, OST presents an opportunity to recruit problem opioid users into treatment, to reduce illicit opioid use and risk behaviors in prison, and

potentially to minimize overdose risks on release. If liaison with community-based programs exists, prison OST facilitates continuity of treatment and longer-term benefits can be achieved. For prisoners in OST before imprisonment, prison OST provides treatment continuity, especially important for drug users who are incarcerated for short periods.

There are also limitations. OST is not suitable for users of non-opioid drugs, nor is it appropriate for drug users who have only recently started to use opioids, even though the early stages of use are associated with high risks of becoming infected with HCV through using another person's paraphernalia. Even in countries with high levels of OST provision, it is unusual for coverage of the total opioid-dependent population to rise above 50–60 % (EMCDDA 2012). While other treatment modalities meet some of the shortfall, there remain important populations of problematic drug users who do not come for treatment, or who do not fare well in treatment. Other approaches need to be pursued alongside or in combination with OST.

Specific risks of OST include the possibility of (methadone) overdose during the early stages of treatment indicating the need for caution over dosages and the advisability of supervised consumption during induction. Methadone overdoses also occur in association with careless prescribing or the use of illicit methadone from diversion or thefts. Different challenges arise from the accumulation of ageing, long-term patients on OST, many with multiple comorbidities. A harm reduction approach includes encouraging OST clients to become drug-free when they can but also accepts that for some, this is not possible.

Several important lessons learned should be stressed. Adequate doses are essential. While individual dosage levels vary, positive outcomes are mostly achieved when average program methadone dosages are in the 60–120 mg range (Faggiano et al. 2003; WHO 2009). Continuity too is vital, accompanied by appropriate psychosocial support and health education. Studies comparing methadone and buprenorphine show that while buprenorphine is effective, it is less effective than methadone delivered at adequate doses (Mattick et al. 2008).

83.2.2 Needle and Syringe Programs

Needle and syringe programs (NSPs) are specialized services that distribute sterile injecting equipment to people who inject drugs. They are usually located close to areas where drug injecting is more prevalent. They are almost always part of a wider network of local services. Their primary objective is to facilitate more hygienic injecting practices and to reduce sharing or reuse of needles, syringes, and other injecting paraphernalia in order to prevent injection-related complications, especially transmission of HIV and HCV. In addition, NSPs serve as important contact points for drug users who have little contact with treatment or other health services. Thus a supplementary objective is to deliver health promotion information and to facilitate access to health care, including OST or other treatment. They routinely distribute condoms and offer advice on safer sex. Some offer non-injecting equipment. NSPs may be equipped to provide testing for infectious

diseases and STDs, as well as vaccination for hepatitis B and basic health care. Dedicated NSPs are usually fixed-site, though may also have mobile units or outreach teams. In some countries, NSPs are implemented through national networks of pharmacies. In other settings pharmacy-based programs and vending machines supplement specialized NSPs. In some countries, NSPs have been established in prisons.

83.2.2.1 Evidence on Effectiveness

A broad body of evidence indicates that NSPs are effective, as part of a multicomponent set of responses, in reducing injecting risk behaviors and in limiting transmission of blood-borne infections, without increasing the prevalence or frequency of injecting (WHO 2004a; Tilson et al. 2006; Department of Health and Human Services 2011). There are methodological difficulties in separating the impact of NSPs from that of other interventions and local contextual factors, which means that rigorous studies of the effectiveness of NSPs as a single intervention are limited. Two early studies in Montreal and Vancouver found negative outcomes in settings where NSPs attracted marginalized, high-frequency cocaine injectors while at the same time operating restrictive policies regarding syringe exchange (Tilson et al. 2006). Otherwise, evidence from systematic reviews of NSPs across a range of settings indicates that they are effective in reducing self-reported risk behaviors associated with injecting (Palmateer et al. 2010; Kimber et al. 2010). Review-level evidence regarding their independent impact on HIV incidence is also positive though more tentative and for HCV is considered insufficient (Tilson et al. 2006; Kimber et al. 2010). A larger number of descriptive studies support the conclusion that NSPs as part of a wider package of responses are associated with reduced HIV incidence and, as noted earlier, several studies suggest that the combination of NSPs and OST is effective in reducing HCV, if coverage of both interventions is adequate (WHO 2004a; van den Berg et al. 2007; Des Jarlais et al. 2010; Turner et al. 2011). There is also evidence that NSPs are cost-effective (Jones et al. 2008; The National Centre for HIV Epidemiology and Clinical Research 2009).

There is some review-level evidence to support the effectiveness of pharmacy access to needles and syringes, in addition to dedicated NSPs, in reducing self-reported injecting risk behavior, and weaker evidence regarding reductions in HIV, though not HCV incidence (Kimber et al. 2010; ECDC and EMCDDA 2011). Scientific evidence on the impact of vending machines is limited but suggests that they can complement NSPs in specific locations by providing 24 h coverage (Islam and Conigrave 2007).

Although rigorous review-level evidence is lacking on the impact of NSPs in prison settings, reviews of descriptive studies in different countries report important reductions in injecting risk behaviors, as well as some evidence that they may limit HIV and HCV incidence (Stöver and Nelles 2003; Dolan et al. 2003; WHO et al. 2007).

There is also evidence that NSPs have a positive impact in terms of facilitating entry and retention in drug treatment (Hagan et al. 2000), improved health care, and reductions in sexual risk behaviors (CDC 2012a).

83.2.2.2 Conclusion

Benefits of NSPs, when implemented appropriately, include important reductions in injecting risk behaviors and HIV transmission. They also play a valuable role in health promotion, sexual risk reduction, and facilitation of access to health care including treatment. In combination with other harm reduction interventions, they can make a significant contribution to reducing not only HIV but also HCV transmission. There is no evidence that the establishment of NSPs encourages non-injectors to start injecting, or that the frequency of injection increases among those who attend them (Tilson et al. 2006). There were no reports of adverse events involving syringes in the studies of prison-based NSPs.

Many important lessons have been learned over the past three decades. It is essential to aim for full coverage of clients' injecting needs. Restrictions on the number of needles and syringes distributed, or insistence on returning used equipment, can be counterproductive, especially for high-frequency injectors such as cocaine users, since this can facilitate reuse and sharing. The underlying principle should be at least 100 % coverage of each injection ("one shot, one syringe") and distribution according to need rather than one-for-one exchange. It is also important to achieve wide coverage of local populations of drug injectors. Many NSPs allow secondary distribution, where clients distribute clean needles and syringes to their partners or peers. Mobile units and outreach are valuable to further extend coverage.

Injecting equipment should be appropriate for the local context and take account of factors such as type and preparation of drugs that are commonly injected. Injectors often have preferences for certain types or sizes of equipment. Apart from needles and syringes, it is necessary to provide other injecting-related paraphernalia, including alcohol swabs, sterile water, filters, mixing vessels (e.g., spoons or "cookers"), and acidifiers (e.g., ascorbic acid or citric acid powders) to assist dissolving the substance to be injected (ECDC and EMCDDA 2011).

Health promotion should cover information on viral infections, how they are transmitted and how they can be avoided, practical advice on hygiene and safer injecting, as well as information on STDs and on ways of reducing sexual risks. It should include provision of condoms, information on health and social services, and, when appropriate, referral to drug treatment. While staff can encourage clients to consider entering treatment, or to change to safer routes of administration, this should not be linked to pressure such as implied withdrawal of services. Since NSPs come in contact with out-of-treatment drug injectors, it is valuable if they have the capability to carry out on-site counselling, testing, and monitoring of HIV, viral hepatitis, STDs, and TB, as well as vaccination for hepatitis B. Some NSPs also provide basic health care (e.g., wound dressing) or overdose prevention education, including naloxone.

It is important to distinguish receptive and distributive sharing. While receptive sharing (borrowing) should be strongly avoided, even if the lender is known to be seronegative, it is even more important that distributive sharing (lending) by persons who are seropositive is prevented. There is evidence that drug users reduce their distributive sharing (and also sexual risk behaviors) if they know that they are

seropositive, even if they do not change their receptive sharing behavior (Des Jarlais et al. 2004). Testing and behavior change counselling are essential, not only for those who are seropositive but also for those who test negative, since it is important to avoid complacency.

Despite advice not to reuse syringes, personal reuse does sometimes occur. If this is thought to be frequent, then the availability of syringes and needles needs to be increased. A second-best (and controversial) suggestion is to teach users to sterilize their equipment using bleach. While effective for HIV in the laboratory, there is insufficient evidence of effectiveness in practice because correct disinfection procedures are not or cannot always be followed, especially in settings such as prison or on the street (Small et al. 2005; ECDC and EMCDDA 2011). Another suggestion has been to make available low dead-space syringes (LDSS) in addition to other syringes. LDSS reduce the amount of blood remaining in the syringe after completely pushing down the syringe plunger (WHO 2012; Zule et al. 2013). However, there is a risk that this may appear to accept sharing, in contradiction to the clear message that syringes should not be reused or shared. The provision of fresh equipment for each injection should be a priority.

Safe disposal of used equipment is important. NSPs can facilitate safe disposal by receiving used syringes or by providing puncture-resistant disposal containers to clients. However, if carrying used needles and syringes is a criminal offence or may be used as evidence of drug use, clients may be reluctant to bring used equipment back.

Accessibility and acceptability to target populations are important. This means setting up NSPs in appropriate locations, with easy access and a minimum of bureaucratic entry requirements. Opening hours should include evenings and weekends. Staff should be positive and sympathetic. Qualified nursing personnel are important, and other staff, including peer workers, need to be trained.

NSPs are mostly implemented in urban settings and areas with a higher prevalence of injecting. In smaller towns and rural settings, a pharmacy-based model may be more appropriate.

Apart from (free) distribution through NSPs, needles and syringes can be purchased at pharmacies in many countries, though various formal or informal restrictions can discourage people from using this option, and even a low price may be a disincentive for low income populations.

The distribution of non-injecting paraphernalia has been suggested for people who smoke heroin or cocaine (Leonard et al. 2008). One pilot study suggested that distributing foil and smoking materials from needle and syringe programs helps to promote transitions from heroin injecting to chasing (Pizzey and Hunt 2008).

Despite clear evidence on the benefits of NSPs, opposition from local policy makers, professionals, and community groups can hinder the establishment of NSPs. Consultation with relevant local bodies is essential. Careful planning and coordination with local health and treatment services is important to establish clear procedures for referral links. Agreement needs to be reached with justice and police officials to avoid counterproductive interventions.

83.2.3 Supervised Drug Consumption Facilities

Drug consumption rooms (DCRs) are professionally supervised health-care facilities where drug users can use drugs in safer and more hygienic conditions (Hedrich et al. 2010). DCRs seek to attract hard-to-reach populations of drug users, especially marginalized groups and those who use drugs on the streets or in other risky and unhygienic conditions. They aim to reduce morbidity and mortality by providing a safe environment for more hygienic drug use and by training clients in safer drug use. At the same time, they seek to reduce public drug use and improve public amenity in areas surrounding urban drug markets. A further aim is to promote access to social, health, and drug treatment facilities. Since 1986, more than 90 DCRs have been set up in seven European countries as well as in Canada and Australia (Hedrich et al. 2010) and are planned in several more. They are highly targeted services addressing specific local problems within a wider network of services. Access is typically restricted to registered service users. They usually operate from separate areas attached to existing facilities for drug users or the homeless, though some are stand-alone units. Most target drug injectors, though increasingly cover users who smoke. At times, they have been controversial due to concerns that they may encourage drug use, delay treatment entry, or aggravate problems of local drug markets, and initiatives to establish DCRs have been prevented by political intervention.

83.2.3.1 Evidence on Effectiveness

Evidence shows that DCRs succeed in reaching their target populations and achieve immediate improvements in hygiene and safer use for clients who use the services. There is consistent evidence that DCR use is associated with self-reported reductions in injecting risk behavior such as syringe sharing as well as reductions in public drug use and nuisance such as discarded syringes (Hedrich et al. 2010). Due to a lack of studies, methodological problems of isolating the effect of DCRs from other interventions, or low coverage of the risk population, there is insufficient evidence on effectiveness regarding reduced HIV or HCV incidence (Kimber et al. 2010). There is evidence that use of the facilities is associated with increased uptake both of detoxification and of OST. There is tentative evidence from ecological studies that DCRs may contribute to reducing drug-related deaths at a city level where coverage is adequate (Hedrich et al. 2010; Marshall et al. 2011). There is also evidence that DCRs are generally accepted (or at least seen as the lesser of two evils) by local communities and officials, albeit with some reservations (Hedrich et al. 2010).

83.2.3.2 Conclusion

Benefits of DCRs include improvements in safe, hygienic drug use, especially among regular clients; increased access to health and social services; and reduced public drug use and associated nuisance. The availability of safer injecting facilities does not increase drug use or frequency of injecting, it facilitates rather than delays treatment entry, and does not result in higher rates of local drug-related crime.

DCRs have mostly been established in specific urban settings with problems of public drug use or where there are subpopulations of drug users with limited possibilities of hygienic injection (e.g., homeless, living in insecure accommodation or shelters). In some cases, DCRs are also utilized for various reasons by more socially stable clients, for example, because they live with non-using partners or families. As with NSPs, consultation with local key actors is essential to minimize community resistance or counterproductive police responses.

83.2.4 Overdose Prevention

Although rising overdose deaths often serve as a catalyst for concern over drug use, efforts to develop specific interventions to reduce overdoses have emerged more slowly than responses to other drug-related problems like dependence, crime, or HIV/AIDS. As noted above, OST significantly reduces overdose mortality, and DCRs may make a contribution at the local level. A promising approach to reducing opioid overdose deaths is offered by community-based overdose prevention programs that include peer naloxone distribution (CDC 2012b).

Naloxone (Narcan®) is an opioid antagonist used in medical emergencies to reverse respiratory depression caused by opioid overdose. It has no effect on non-opioid drug overdoses and has a high safety margin. It is available in an injectable form and, in the USA and some other countries, as an intranasal spray.

The aim of naloxone distribution programs is to increase the availability of effective medication in places where overdoses are more likely to occur. The rationale is that overdose is common among opioid users. In some studies, over a third have experienced an (nonfatal) overdose and two-thirds have witnessed one (Lagu et al. 2006). Many people who die from opioid overdose fail to receive proper medical attention because their peers and other witnesses (often other drug users) do not recognize the seriousness of the situation and delay or do not call emergency services for fear of police involvement (Pollini et al. 2006).

Peer naloxone distribution programs work by training drug users and other likely first responders (peers, families) as well as frontline services such as health-care providers, staff in homeless shelters, and in some cases police officers on how to recognize and respond to an overdose, including the administration of naloxone, until emergency medical help is obtained. In the USA, the first program began distributing naloxone in 1996. The number of programs has subsequently risen to at least 50 in 15 states (CDC 2012b). Programs are also reported in other countries including the UK and Australia (Strang et al. 2008; Kerr et al. 2009).

83.2.4.1 Evidence on Effectiveness

Review-level evidence is lacking, but studies indicate that peer naloxone distribution is feasible (Strang et al. 2008; CDC 2012b). Evidence on impact suggests that it can be effective in reducing overdose deaths at community level (Maxwell et al. 2006; Walley et al. 2013). A survey of 48 programs across the USA concluded that distribution of naloxone and training in its administration might have prevented

numerous deaths from opioid overdoses (CDC 2012b). There have been questions of whether nasal administration is as effective, but several studies have found that it can be used safely and effectively outside of hospital settings (Kerr et al. 2009; Doe-Simkins et al. 2009), including on a take home basis (CDC 2012b). A recent study suggests that naloxone distribution is cost-effective (Coffin and Sullivan 2013).

83.2.4.2 Conclusion

Potential benefits include substantial reductions in opioid overdose deaths, if sufficient coverage of risk populations can be achieved. It is recommended by CDC in the USA and by the Global Fund to Fight AIDS, TB and Malaria as a component of a comprehensive package of services for drug users.

In most jurisdictions, naloxone is a prescription only medicine and its use is restricted to medical personnel or to patients to whom it is prescribed. It is thus necessary to change regulations to enable administration by laypeople, as has occurred, for example, in several US states (CDC 2012b). The risks are low as it is a safe drug and there is no evidence that it may encourage risky drug taking. Administration via nasal spray offers advantages for nonmedical responders. Further information is available in a manual developed by the Harm Reduction Coalition (2012).

Even if naloxone distribution is not feasible, increasing risk awareness and response skills among professionals in contact with drug users, and disseminating information to users, their peers, and families, constitutes an important part of a comprehensive program to reduce overdose mortality. Prison release or treatment discharge counselling on overdose risk should be a key component. Crisis intervention and counselling at hospital emergency rooms following admission for overdose have been tried in some countries. New online tools can be used for awareness raising and risk assessment. Precautions over prescribing opioids (especially together with CNS sedatives) are also important, since in the USA a significant proportion of drug overdose deaths are associated with prescription opioids and sedatives (CDC 2013).

83.2.5 Outreach, Peer Education, and Health Promotion

Community-based outreach aims to facilitate improvements in health and reductions in risks and harms for individuals and groups who are not effectively reached by fixed-site services or through traditional health education channels (Rhodes and Hartnoll 1991; Needle et al. 1998, 2005; NIDA 2000; WHO 2004b). It seeks to achieve this through identifying and contacting target groups of drug users in different community settings in order to deliver in situ interventions to hard-to-reach populations, as well as to provide a contact point for increasing access to a range of other services. Depending on the circumstances, interventions may include dissemination of information on drug- and sex-related harms and risk behaviors, provision of advice and counselling on individual behavior change, distribution of sterile injecting equipment and condoms, overdose prevention training including naloxone distribution, and measures to facilitate access to health care, social services, and drug treatment.

Outreach projects may operate from a stand-alone base but are often attached to community health and social services such as NSPs, street-level low-threshold services, treatment centers, etc. Target groups include homeless, migrant or minority group users with limited access to services, street users, sex workers, chaotic stimulant and multiple drug users, or more private, closed groups.

Many variants of outreach have been described (Rhodes and Hartnoll 1991, 1996; NIDA 2000; Needle et al. 2005). Some are based on professional youth or community health workers, others originated from ethnographic research involving indigenous leaders to target at risk networks and individuals, others have focused on promoting peer-driven outreach, and others have developed out of advocacy or self-help organizations. Some concentrate on the individual level (information and awareness raising, referral or support for change), while others give greater emphasis to a network approach involving peer education and modification of peer norms or empowerment of vulnerable groups.

83.2.5.1 Evidence of Effectiveness

A review of over 40 studies of outreach interventions to prevent HIV infection among injecting drug users concluded that outreach is an effective strategy for reaching hard-to-reach, hidden populations of IDUs and provides the means for enabling IDUs to reduce their risk behaviors. A significant proportion of IDUs receiving outreach-based interventions reduced their risk behaviors (drug using, needle and sexual practices) and increased their protective behaviors. Uptake of voluntary testing, counselling, and drug treatment was also increased through referral from outreach teams (Needle et al. 2005). This confirms earlier studies of outreach effectiveness (Stimson et al. 1998).

Peer group social norms about modes of drug use, including the sharing of injecting equipment, have a strong influence on behavior (Grund et al. 1996). In the early stages of the HIV epidemic among injecting drug users in the USA, users were already changing their risk behaviors prior to formal interventions (Des Jarlais et al. 1988). This has encouraged peer-based outreach to focus on changing social norms regarding safer behavior as well as on individual change (Latkin et al. 2003).

Studies of network approaches suggest that, given guidance and nominal incentives, injecting drug users can play a more extensive role in community outreach efforts than the traditional model allows. While both traditional and peer-driven interventions reduce HIV-associated risk behaviors, peer-driven outreach reaches a larger and more diverse set of drug injectors and does so at less expense (Needle et al. 1998).

83.2.5.2 Conclusion

Outreach is a flexible and effective component of local harm reduction strategies. It is essential that outreach workers can establish rapport with target populations and gain acceptance as trusted and knowledgeable sources of information and advice. It is vital to ensure confidentiality and to communicate messages clearly. Outreach workers need adequate training, support, and protection, especially in peer-driven interventions. This is helped by clear guidelines covering objectives,

services offered, responsibilities, and limits (personal, professional, legal, etc.) (NIDA 2000). Concrete procedures with other local agencies are important to maximize the uptake of referrals. Drug users and user organizations should be actively involved as partners in planning and conducting outreach.

83.2.6 Testing, Vaccination, and Treatment of Infectious Diseases

Public health guidelines recommend a comprehensive approach to prevention and treatment of infectious diseases among high-risk populations. This chapter highlights selected key points of relevance to practitioners and managers involved in harm reduction interventions for problem drug use. Extensive information on public health policy, scientific evidence, and clinical practice can be found in reviews and guidelines published by public health institutions (e.g., ECDP and EMCDDA 2011; CDC 2012a; WHO 2012).

Recommended core measures include provider-initiated offer of voluntary, confidential screening for HIV, hepatitis B and C, common STDs, and TB; vaccination for hepatitis A and B and where clinically indicated for tetanus, influenza, and pneumococcus (HIV positive); and antiretroviral treatment (ART) for HIV, as well as treatment for STDs, TB, and hepatitis C. Care should be taken about potential medication interactions, including methadone, especially in the treatment of people with coinfections.

Testing offers the opportunity to provide information and health education to all clients, as well as to identify cases for vaccination or treatment. Knowledge of serostatus provides an informed basis for discussing changes in drug use and sexual behavior with clients and has been found to be associated with positive behavior changes (Des Jarlais et al. 2004, 2010). A study in 20 cities across the USA in 2009 reported 9 % prevalence of HIV among people who inject drugs, of whom 45 % did not know that they were positive (CDC 2012c). Testing of clients can also provide opportunities to encourage partners to be tested and to participate in changes needed to reduce risks. Periodic health checks and monitoring of seronegative individuals can help reinforce protective behaviors. It also contributes to monitoring program effectiveness.

Antiretroviral treatment (ART) is now a highly effective treatment for HIV. It not only benefits individuals but has important preventive effects, since it reduces infectivity and thus the risk of transmission to others (WHO et al. 2013). ART during pregnancy sharply reduces viral load and risk of mother to child transmission of HIV (WHO 2010). When used consistently, ART preexposure prophylaxis has been shown to be effective in men who have sex with men (MSM) and heterosexually active men and women. Trials are under way to assess its effectiveness for drug injectors (CDC 2012a).

Treatment of hepatitis C is effective though expensive. Drug use per se is not now considered to be an exclusionary criterion (WHO 2012). Adherence to treatment is improved through accompanying OST and social-psychological support (this applies to ART also) (ECDC and EMCDDA 2011). Given the challenges of

preventing HCV, treatment of hepatitis C offers an alternative long-term preventive approach. The development of new drugs may make treatment as prevention a realistic goal in the future.

Universal vaccination of children for hepatitis B and vaccination campaigns targeting high-risk groups mean that hepatitis B should become increasingly rare in the future (the USA and the EU have eradication plans). Meanwhile, it is valuable to continue screening for HBV and where appropriate offer vaccination using the Accelerated Schedule (WHO 2012).

STDs increase the risk of sexual transmission of HIV by a factor of 2–5 (CDC 2010). Thus identification and treatment of common STDs is one of the principle HIV prevention strategies among sexually active individuals, especially in high-risk populations (Tilson et al. 2006).

Access to and uptake of testing and treatment of infectious diseases and STDs can be increased by developing on-site screening at services for drug users such as drug treatment centers or NSPs. Rapid testing techniques now make this feasible in a variety of contexts, including low-threshold services and outreach. Where possible, treatment delivery should take place at the same sites to improve uptake. If this is not possible, then active referral pathways to public health facilities should be established. Rapid HIV testing kits (OraQuick) for home use have now been approved by the FDA in the USA and are available from major pharmacies. This further extends prevention possibilities.

83.2.7 Interventions for Stimulant Use

There is a substantial literature on harms that can arise from heavy use of cocaine or amphetamine-type stimulants (Grund et al. 2010). However, many harm reduction interventions are based on models developed in response to opioid use. Less information is available on interventions that specifically target harms of stimulant use.

Apart from dependence, harms associated with chronic stimulant use include a variety of cardiovascular, pulmonary, or neurological damages; mental health problems such as acute psychotic episodes; chaotic behavior, including higher rates of needle sharing associated with intensive, high-frequency injection; increased risk of HIV and STDs linked to high-risk sexual activity (Colfax and Shoptaw 2005); and increased risk of HIV and HCV associated with cocaine smoking, both through sharing paraphernalia and through sexual contact. In high cocaine prevalence areas, significant numbers of acute cocaine episodes are seen by medical emergency services, and cocaine (injected or smoked) is reported in a majority of overdose deaths, often in combination with opioids (CDC 2012a).

The likelihood of harm varies according to context. For example, crack cocaine use is most likely to be found among highly marginalized groups and is associated with elevated levels of risk of transmission of HIV, especially for women who trade sex for money or drugs (Booth et al. 2000). Crack is sometimes injected as well as smoked, adding a further risk dimension (Rhodes et al. 2006). Transmission of

HCV may also occur through sharing of crack pipes via oral sores and cracked lips (Fischer et al. 2008). Methamphetamine use, especially by men who have sex with men (MSM), is associated with high levels of sexual risk behavior (Shoptaw and Reback 2006; CDC 2012a). High levels of cocaine use may also be found among more socially integrated users who sniff rather than inject or smoke the drug. While health risks associated with this route of administration are lower, they still remain, especially through higher sexual risk behavior and possibly through sharing straws. The social networks and economic resources of more socially integrated cocaine users may enable them to resolve problems without contacting services (Decorte 2000). For the most part, problem stimulant use seen at public services is associated with lower socioeconomic status and a range of social and legal problems, in addition to a variety of psychiatric comorbidities (Grund et al. 2010).

Harm reduction interventions available for stimulant users include psychosocial treatment, NSPs, outreach and peer-driven programs, sexual risk reduction education, information campaigns including web-based dissemination, crack kits, assertive community treatment, environments to reduce anxiety and increase control over use, as well as approaches based on alternative medicine. ART preexposure prophylaxis may also be relevant for high-risk sexual behavior.

83.2.7.1 Evidence on Effectiveness

Apart from treatment evaluations, there are few high-quality scientific studies of interventions to reduce specifically the harms of stimulants. Systematic reviews indicate that outpatient treatment including contingency management, cognitive behavior therapy, or motivational interviewing offers modest improvements, more so when interventions are multimodal and intensive (De Lima et al. 2002; Knapp et al. 2007; EMCDDA 2010). Retention rates in treatment tend to be low, reducing the potential for systematic efforts to reduce risk behaviors.

Existing interventions that partially cover stimulant-using populations (mostly of cocaine) include OST for those who also use opioids. While many clients benefit from OST in terms of reduced cocaine use, continued cocaine use has a disruptive effect on OST outcomes (Williamson et al. 2006). Research has yet to confirm effective specific pharmacological treatments, and work on a cocaine vaccine progresses slowly. There is no established equivalent of OST for stimulant users. There have been preliminary studies of substitution treatment with dexamphetamine or modafinil (Castells et al. 2010), and a recent translational review suggests that agonist replacement therapy, especially monoamine releasers, may be effective for managing cocaine dependence (Rush and Stoops 2012), especially if novel compounds or formulations that have less misuse and diversion potential can be identified.

NSPs can be effective for injecting stimulant users as well as for opioid users. As noted earlier, stimulant injectors inject frequently and need a plentiful supply of sterile syringes and needles. Given the chaotic lifestyle, frenetic drug using behaviors, and disturbed sleep patterns often seen in compulsive stimulant injectors, providing adequate coverage of injecting needs, potentially for up to 24 h per day, is a challenge for any service. Mobile units and syringe dispensing machines can help extend coverage in terms of times and places.

Most DCRs were initially established for heroin injectors and often did not admit cocaine injectors or smokers. Increasingly, these facilities adapt to client needs and have set up separate rooms for smokers of cocaine or heroin. This has proved to be feasible, attracting important subgroups such as crack-using sex workers, and appears to provide benefits similar to those that obtain for heroin users (Hedrich 2004; Grund et al. 2010).

It has been suggested that traditional harm reduction services fail to reach problem stimulant users due to opiate-centered services and social barriers to young or female users (Grund et al. 2010). Greater emphasis needs to be placed on outreach and peer education approaches (see above), especially for younger users. For example, a peer-run, all night street NSP in Vancouver was able to deliver harm reduction services to the city's most vulnerable cocaine injectors (Wood et al. 2003). An unpublished PhD thesis by Henskens on a randomized controlled trial of Assertive Community Treatment for marginalized crack users in Rotterdam indicated good program compliance and improvements in physical and mental health (Grund et al. 2010).

In response to the risks associated with smoking crack, some programs in the USA, Brazil, Canada, and France have developed "crack kits". These include a Pyrex tube, plastic tips, filters, lip balm, sterile compresses, chewing gum for salivation, and condoms. Initial results suggest that sharing of crack pipes decreased dramatically, while crack users reduced injecting and more often smoked cocaine (Leonard et al. 2008). However, crack kits are controversial and rarely funded.

Regarding crack, there is some evidence that the severity of mental health harms associated with cocaine is related more to the intensity and context of use than to the specific form of cocaine used (Haasen et al. 2005). Harm reduction measures aimed at safer, more controlled, less intensive use of cocaine together with steps to stabilize the social situation may help to decrease mental health problems.

Other approaches include acupuncture as an adjunct to treatment to reduce craving, though a systematic review of controlled trials found no evidence of effectiveness (Gates et al. 2006), or providing accessible and flexible walk-in calming environments to reduce agitation and anxiety levels (Grund et al. 2010). Advice, counselling, and treatment services for socially integrated users may be more attractive if separated from services for opioid users and drug injectors and if they operate at appropriate hours, for example, evenings. Interventions for less intensive users include information dissemination on managing mental health risks or on stimulant use via flyers or websites, personal messaging via mobile phones, or "pill-testing" in nightlife settings.

83.2.7.2 Conclusion

Patterns of stimulant use and risks can vary greatly from one setting to another. For example, in some former Soviet Union republics, home production of stimulants is associated with specific and highly risky patterns of drug consumption (Grund et al. 2010), and in the UK, groin injection of crack cocaine raises special

challenges (Rhodes et al. 2006). In some settings, women are particularly at risk. This means that interventions need to be thoughtfully planned to take account of local circumstances and vulnerable groups. This should include critical reflection on whether any unintended negative effects might arise. While there is much room for innovative development of harm reduction responses, it should be stressed that all interventions for stimulant users need to give high priority to sexual as well as drug-related risks.

83.2.8 Drug-Related Sexual Risk Reduction

Many harm reduction interventions concentrate on drug-related risks but overlook sexual risks. Since many patterns of drug use, injecting and non-injecting, are associated with elevated risks of contracting or transmitting STDs including HIV, all interventions should if possible include sexual as well as drug risk reduction components. Priority targets for more intensive efforts include sex workers, stimulant users, MSM, female crack users, and partners of HIV-/HCV-positive users. Some of the risk factors and settings associated with elevated sexual risks have been mentioned earlier in this chapter.

Apart from testing and treatment of STDs, interventions to reduce sexual risks include condom distribution and information, education, and counselling. These can be carried out at drug treatment centers, NSPs, STD clinics, and low-threshold services including outreach and peer education. ART preexposure prophylaxis is now also becoming a possible option. The Internet, social media, and mobile phone messaging offer new means of communicating health counselling and advice.

Evidence suggests that condom distribution among young or high-risk populations in general is effective in terms of increasing condom use and reducing STDs (CDC 2012a). Interventions improving the availability of condoms in specific risk settings or increasing their accessibility among risk groups, as well as including additional individual, small-group, or community-level components along with condom distribution, were shown to be efficacious in increasing condom use behaviors. Free distribution facilitates availability and accessibility.

Sex risk education and counselling is also effective (Semaan et al. 2002, 2010; Meader et al. 2010, 2013). Systematic reviews show that significant reductions in sexual risks can be achieved through standard, relatively brief educational interventions and that multi-session psychosocial interventions offer only modest additional benefits. People in formal treatment are more likely to respond to multi-session psychosocial interventions. It also appears single-gender groups may be associated with greater benefit. Generally, brief standard education interventions appear to be a more cost-effective option.

It is important to stress the importance of gender sensitive interventions, given the higher risks and vulnerability of many women problem drug users. More intensive efforts are necessary to empower women to be able to adopt safer sexual practices with partners or clients.

83.3 Conclusion

This chapter has provided an overview of different interventions that contribute to reducing drug-related harms. Harm reduction does not replace the need for treatment but adds to our capacity to respond effectively to the wide range of health and social challenges raised by drug use. It is clearly established that single interventions are far more effective when implemented together as part of a broader package, including steps to facilitate enabling environments that foster healthier and safer living. Combining interventions into a coherent harm reduction approach is covered in ▶ Chap. 84 "Harm Reduction Policies, Settings, and Challenges" in this textbook.

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Harm Reduction Policies, Settings and Challenges

84

Richard Hartnoll and Dagmar Hedrich

Contents

Abstract

Harm reduction has become an increasingly important dimension of drug policy over the past three decades. This chapter describes what harm reduction is and how harm reduction policies take account both of individual risk behaviors and of risky settings in order to promote improvements in individual and public health and societal well-being. Another chapter in this textbook, ▶ Chap. 83, "Harm Reduction Interventions", gives an overview of specific interventions.

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This chapter covers the following: what harm reduction is, its history and current status from an international perspective, drug-related harms, risk behaviors, risk settings, harm reduction as a combination intervention, implementing an integrated approach at local level, needs assessment in local settings, enabling environments, epidemiological settings, prison settings, law enforcement settings, overcoming barriers, and promoting health and equality of care. It concludes that harm reduction policies and interventions have been successfully implemented in many countries around the world; that over the past two decades, political and professional opinions have increasingly promoted a "comprehensive approach" that includes harm reduction as a central pillar; and that while heroin use and related problems, as well as HIV among drug injectors, are now largely under control in countries that have implemented comprehensive harm reduction policies, challenges remain in those and other countries, including hepatitis C, problems related to stimulant drug use, and continuing sexual transmission of infectious diseases related to drug use. Apart from client-oriented skills, practitioners need an understanding of the community and public health settings within which drug use and drug-related harms arise.

84.1 Introduction

Harm reduction has become an increasingly important dimension of drug policy over the past three decades. The chapter in this textbook, ▶ Chap. 83, "Harm Reduction Interventions," gives an overview of specific harm reduction interventions. This chapter describes what harm reduction is and how harm reduction policies take account both of individual risk behaviors and of risky settings in order to promote improvements in individual and public health. It also stresses harm reduction as a combined response and the importance of a comprehensive, integrated approach.

84.2 Policies, Settings, and Challenges

84.2.1 What Is Harm Reduction?

Harm reduction is a multidimensional response encompassing interventions, programs, and policies that seek to reduce the health, social, and economic harms of drug use to individuals, communities, and societies (Rhodes and Hedrich 2010). Harm reduction policies are also found in related areas of public health and social policy, for example, alcohol policy, safe sex, or nicotine replacement.

Harm reduction is based on the concept of harmful drug use. This is wider than, though includes, the concept of dependence. It does not assume that drug use per se is harmful. It can be seen as a pragmatic approach in which the goal is to reduce the harmful consequences of drug use through a package of evidence-based, targeted interventions tailored to local settings and needs. Harm reduction programs

typically work through a hierarchy of goals in which the most pressing needs are addressed first (IHRA 2010).

Drug-related harm refers both to individual consequences such as dependence, overdoses, or infectious diseases contracted through sharing paraphernalia and to social, economic, and public health harms to the community (public nuisance, crime, health-care costs, high HIV prevalence). The underlying public health paradigm is broader than client-centered treatment and involves balancing individual and societal needs.

A harm reduction policy entails a "combination intervention approach" involving a coordinated response from a variety of agencies and services, including treatment, prevention, public health, law enforcement, community groups, and local authorities (Rhodes and Hedrich 2010; ECDC and EMCDDA 2011; WHO et al. 2013). This approach goes beyond interventions for individuals by stressing enabling environments to enhance protective factors, reduce harms, and promote public health.

Harm reduction incorporates an important ethical dimension concerning human rights, equality of access to health and social services, respect of the right to privacy and confidentiality, and efforts to counteract social exclusion and stigma (IHRA 2010; Jürgens et al. 2010).

It also acknowledges that important unintended negative consequences can arise from reactions to drug use (European Commission 2009; UNODC 2009). These include structural factors such as the wider policy and legislative framework as well as risk environments that increase social exclusion of already marginalized sections of the community, foster reluctance to seek help for fear of arrest, or exacerbate the HIV epidemic among drug users (Rhodes 2009; Wood et al. 2009; Degenhardt et al. 2010).

84.2.2 History and Current Status

Early examples of harm reduction include the so-called British System of opiate maintenance for patients who, while capable of "leading a useful and fairly normal life" on a stable dose of the drug of addiction, were unable to do so when the regular allowance was withdrawn. In the early 1970s, various ad hoc harm reduction responses evolved at grass roots level in some western European cities (street agencies, outreach, user-driven organizations, and information dissemination). Methadone maintenance, which had originated in the USA, was introduced in a handful of European countries.

Harm reduction as a policy started to gain wider acceptance in Europe with the emergence and rapid spread of HIV/AIDS among drug injectors in the mid-1980s. For example in Britain, the spread of HIV was seen as "a greater danger to individual and public health than drug misuse" (ACMD 1988). The WHO also endorsed the underlying principles of harm reduction (WHO 1986). From 1985, opioid substitution treatment (OST) expanded to more mostly western European countries, and needle and syringe programs (NSPs) were progressively introduced.

Over the 1990s both OST and NSPs extended, albeit unevenly, to most countries including central and eastern Europe (Hedrich et al. 2008).

Beyond Europe, harm reduction approaches emerged in countries such as Australia and Canada (Pates and Riley 2012). Harm reduction interventions also developed in the 1980s in some US cities such as San Francisco (Watters et al. 1994), Chicago (Wiebel 1996), and New York (Des Jarlais et al. 1988) though opposition from federal government and influential lobbies meant that they were not described as such.

Harm reduction is now a major pillar of drug policy in all EU member states (Hedrich et al. 2008) and globally is supported by at least 97 countries (Stoicescu 2012). It is firmly established as a mainstream systemic response promoted in official declarations by the WHO, United Nations, and European Union as a key element of a comprehensive approach (Council of the European Union 2003; WHO et al. 2013).

Within these overall developments, the range of interventions and scale of implementation vary considerably between and within countries (Mathers et al. 2010; Stoicescu 2012). For example, in Europe OST covers over 50 % of opioid-dependent users across most of the continent, though in a few countries coverage is under 20 %. Syringe distribution by NSPs ranges from under 50 per user per year to over 300 (EMCDDA 2012a).

Harm reduction developed mainly in response to public health consequences of heroin use and drug injecting. In many parts of the world, serious problems arise from heavy stimulant use, especially cocaine and methamphetamine. In Europe, the USA, and other countries, an ageing population of chronic users poses new challenges (EMCDDA 2010; ▶ Chap. 128 "Older People and Substance Misuse").

Strong religious, ideological, and political resistance remains in some countries and within some institutions. Sometimes interventions are implemented but not called "harm reduction." In other cases, evidence-based harm reduction interventions have been blocked, with serious consequences. In Russia, for example, methadone was declared illegal, despite urgings to the contrary (UNAIDS 2005). From 1995, injection-related cases of HIV in Russia rose rapidly and since 2002 account for over 80 % of all cases of HIV (Goliusov et al. 2008). Conversely, the role of user groups and advocacy organizations has been changing from opposition to mainstream policies towards recognized and constructive participation in developing evidence-based interventions to reduce drug-related harm (Stoicescu 2012).

84.2.3 Drug-Related Harms

Much drug-related harm occurs in association with heavy or regular consumption of opioids, central nervous system (cns) stimulants, or multiple drug combinations, including alcohol and other cns depressants. There is also a strong relationship between drug injecting and more severe levels of harm, though problems can arise from other routes of administration.

84.2.3.1 Drug-Related Morbidity

Dependence is the most likely consequence of regular drug use seen by professionals in treatment facilities, criminal justice settings, or general practice. Treatment of dependence is covered in other chapters. It should be noted, however, that levels of risk associated with unsafe injecting and with unsafe sexual behaviors increase with higher severity of dependence (Gossop et al. 1993a, b). It is also important to stress that for people who progress from experimental or intermittent drug use to injecting or more intensive patterns of use, there is usually a time lag of several years before they contact treatment services. During these early stages of a drug-using career, individuals may be especially at risk of contracting viral infections such as hepatitis C (Maher et al 2007). This underlines the importance of efforts to reach recent initiates with effective harm reduction and health promotion interventions. By the time they contact treatment services, it may often be too late.

Blood-borne viral infections such as HIV and hepatitis (especially HCV) constitute an important component of injection-related morbidity (see ▶ Chap. 106, "Substance Use and Co-Occuring Infections: An Overview"; ▶ Chap. 102, "Liver Disorders (Incl. Hepatitis) in IVDAs"). Prevalence and incidence of HIV and viral hepatitis among drug injectors varies considerably between sites and over time. For example, HIV prevalence among drug injectors ranges from under 5 % in most northern European countries to over 35 % in parts of eastern Europe and Russia (Mathers et al. 2010; Jolley et al. 2012). Hepatitis C prevalence is considerably higher among drug injectors, reflecting the greater transmissibility of this virus, and ranges from 40 % to over 90 % depending on location and duration of injecting (Hagan et al. 2008). Compared to HIV infection, hepatitis C infection is characterized by relatively high concentrations of virus in the blood, not only during the initial infection phase, but also in the majority who become chronically infected. In the United States, 9–12 % of all new HIV cases and 50 % of all new hepatitis C cases are associated with injecting illicit drugs (CDC 2012a). Given the long-term burden of disease and the high treatment costs associated with hepatitis C, prevention efforts should be given high priority. Coinfections with more than one type of hepatitis or with HIV and HCV present growing challenges (WHO 2012).

Other morbidity includes vein damage, abscesses, and cellulitis (ECDC and EMCDDA 2011). Rates of tuberculosis (TB) and sexually transmitted diseases (STDs) are also often substantially higher in drug-using populations (CDC 2012a).

84.2.3.2 Drug-Related Mortality

Reviews of studies in different countries on mortality among problem drug-using populations (mostly opioid dependent) suggest that all-cause mortality is between 1 % and 2 % per annum, 10–20 times higher than among the general population of the same age and gender (Degenhardt et al. 2011; EMCDDA 2011). Drug overdoses, often involving opioid-cns depressant combinations, are the most common cause of death, accounting for about one third to a half of all deaths. In some countries, cocaine is commonly reported in fatal overdoses, often in combination with opioids. Disease, suicide, and trauma are the other main causes of death.

Risk of death is several times higher among injectors than non-injectors. Specific contexts associated with dramatic increases in overdose mortality are the weeks immediately following release from prison, discharge from inpatient detoxification, and dropout from OST (Davoli et al. 2007; Merrall et al. 2010). In the USA, drug overdose deaths more than doubled from 16,849 in 1999 to 38,329 in 2010 (Jones et al. 2013). Prescription opioids in particular, as well as cocaine and heroin, were a major component of this (CDC 2013). Among older, chronic users, comorbidities, including alcohol and liver and cardiovascular diseases, become more important (EMCDDA 2010).

84.2.3.3 Drug-Related Crime

Drugs and crime are related in different ways, including offenses against drug laws (possession, production, trafficking), crimes committed under the influence of drugs (violence, driving), revenue raising crimes to finance drug use (theft, drug dealing), "systemic" crimes related to the illicit drug market (corruption of officials, turf war violence, money laundering), and public order offenses related to street drug scenes and public drug use. Studies have attempted to quantify the social and economic costs of drug-related crime (Godfrey et al. 2002). Harm reduction interventions have mainly focused on drug-related crime that harms local communities, in particular revenue raising crime (drug dealing and theft) and public nuisance arising from visible street drug scenes and markets. Crimes committed under the influence of drugs overwhelmingly involve alcohol, which is not covered in this chapter.

Other social and economic harms include impact on families, employment prospects, community well-being, or local economy. While important, these aspects have been less systematically studied and there is no space to cover them here.

84.2.4 Risk Behaviors

Serious health risks (infections, overdoses) are associated with drug injecting. HIV and especially HCV are efficiently transmitted via the sharing of injecting equipment. Risks arise not only through sharing syringes and needles but also through other materials used to prepare drugs for injection, for example, water, spoons, drug solutions, or filters (ECDC and EMCDDA 2011). Measures sufficient to prevent HIV transmission may not be enough to prevent HCV transmission. Risks also accompany non-injecting use, including bridging between injecting and non-injecting drug use populations, transmission through sharing non-injecting materials (pipes, straws), or sexual transmission (Strathdee and Stockman 2010; CDC 2012a).

Drug use, whether by injection or not, is strongly correlated with unsafe sexual practices, including unprotected sex, multiple partners, and, in some cases, selling sex for money or drugs (CDC 2012a, b). The sale of sex for money or drugs is most clearly associated with severe dependence on heroin or crack cocaine. Use of

stimulants, for example, methamphetamine, is associated with increased sexual activity, including unprotected sex and number of partners, as well was with increased rates of HIV and other STDs (Colfax and Shoptaw 2005; Scheinmann et al. 2007). The high risks linked to methamphetamine use by men who have sex with men have been emphasized in several studies (e.g., Molitor et al. 1998, 1999). For all groups, STDs (e.g., genital herpes or syphilis) substantially increase the risk of HIV sexual transmission (CDC 2010).

Comorbidity of drug dependence and mental disorders is common among problem drug users (see ▶ Chap. 117, "Co-Occuring Mood and Substance Use Disorders", ▶ Chap. 119, "Comorbid Anxiety and Alcohol or Substance Use Disorders: An Overview", ▶ Chap. 124, "Personality Disorders and Addiction Disorders"). There is consistent evidence that depression in particular is associated with increased risk behaviors such as sharing injecting equipment (Stein et al. 2003).

84.2.5 Risk Settings

Individual risk behaviors occur within a wider social context. A variety of environmental factors give rise to structural and situational settings that influence differentially not only harms associated with drug use but also access to health and social care (Poundstone et al. 2004; CDC 2012a). The diversity of settings implies a diversity of risks and responses (Hartnoll et al. 2010). Social exclusion and stigma are potent factors linked to a mix of poverty, unemployment, lack of health care, low life expectations, and discrimination. Racial and ethnic disparities persist regarding drug-related harms and utilization of health care and treatment (CDC 2012a). Criminalization and law enforcement policies often disproportionally target marginalized groups and communities. These structural factors can lead to environments that encourage high rates of risk behaviors and infection among drug users (Rhodes et al. 2005; Rhodes 2009; Strathdee et al. 2010). For example, a policy of arresting drug users with syringes can create situations in which there is a high risk of hasty injecting in unhygienic conditions with shared syringes (Werb et al. 2008). Fear of arrest or of children being taken into care can act as powerful deterrents to contacting treatment or social services among communities who already lack equal access to services. Legislation restricting syringe provision or availability of specific treatments can increase risk behaviors, morbidity, and mortality (Wood et al. 2009).

Given the high rates of arrest and incarceration found among heavy drug users, prison and other institutional settings constitute important risk environments. Although the frequency of drug use and injecting usually diminishes during imprisonment, when it does occur it is often under more risky circumstances than in the community, due to a shortage of syringes, need for secrecy, and the higher prevalence of infectious diseases in prison populations (Darke et al. 1998). Other high-risk situations include interruptions to treatment due to short periods of

imprisonment (Dolan et al. 2005) and release from prison or discharge from drug-free treatment (see 63.2.3.1 above).

Women who use drugs are often at higher risk than men due to various factors related to gender, power relations, and sexual risk. Female injecting drug users are doubly at risk for HIV infection via unprotected sex and unsafe injections and have needs that are often not adequately addressed in HIV-prevention strategies (El-Bassel et al. 2010). In some studies, unsafe sex is a more significant risk factor for women than drug use (Strathdee et al. 2001). Women who inject drugs are more likely to require assistance injecting and to engage in sex trading and unsafe sex. They are also more likely than men to have a regular partner who injects or is HIV positive. Intimate partner violence is much more common for female drug users than non-drug users. Women who have experienced such violence are less able to negotiate safe sex, less likely to use condoms, and more likely to share needles, to have more sexual partners, and to trade sex for money or drugs, including unprotected sex with dealers (Shannon et al. 2008; Folch et al. 2013). Higher levels of psychiatric comorbidity contribute to heightened HIV risk (Gilchrist et al. 2011).

Other contextual risk factors include the prevalence of infectious diseases in local drug-using populations (see later), historical or cultural patterns of drug use including routes of administration and risk behaviors pertaining in given communities (Des Jarlais et al. 1988; Grund et al. 1996), and local drug market conditions regarding what products are available, in what form and with what variability in content (de la Fuente 1996; Topp et al. 2003).

84.2.6 Harm Reduction as a Combination Intervention

A recurrent theme in the overview of single interventions in ▶ Chap. 83, "Harm Reduction Interventions" is the importance of combined or multiple intervention approaches as central to the effectiveness of individual responses (van den Berg et al. 2007; Degenhardt et al. 2010; Turner et al. 2011; Kidorf et al. 2011; Hagan et al. 2011). For example, analysis of data pooled from six cities in the UK suggested that exposure to OST or high NSP coverage approximately halved the risk of HCV infection, while the combination of OST and high NSP coverage could reduce HCV incidence by up to 80 % (Turner et al. 2011). Adherence to antiretroviral treatment (ART) or hepatitis C treatment is facilitated by OST together with psychosocial support (ECDC and EMCDDA 2011). Reductions in sexual and drug-related risks among highly marginalized groups are best approached through intensive community outreach backed up by syringe and condom distribution and improved access to health services, treatment, and social support. The central elements of a multiple-intervention approach recommended by international and national guidelines include the interventions described in ▶ Chap. 83, "Harm Reduction Interventions" (ECDC and EMCDDA 2011; CDC 2012a; WHO et al. 2013), though only the European guidelines mention drug consumption rooms (DCRs), which have more localized relevance and are still controversial in some countries.

84.2.7 Implementing an Integrated Approach at Local Level

While comprehensive national drug policies exist in most countries, it is at local level that the interface between drug use, policies, and responses takes place. Responding to a diversity of issues, from public concentrations of heroin and cocaine use and drug markets in specific urban areas to less visible patterns of problematic drug use distributed across different groups in different sections of the population, is a complex task. Coordination of local policies and interventions is essential due to the range of agencies involved, including health, social services, education, housing, police and criminal justice system, politicians, as well as civil society including nongovernmental organizations, community groups, and user organizations.

Optimizing the benefits obtained from combined interventions implies implementing at local level a coherent package of harm reduction approaches to problem drug use. This poses many challenges. It involves achieving understanding and cooperation between different sectors and organizations operating at different levels and with different agendas. Broader issues of health system organization are beyond the scope of this chapter. The remainder of this chapter focuses on practical questions concerning implementation of multiple harm reduction interventions in different settings.

84.2.8 Needs Assessment in Local Settings

There can be large differences between settings in terms of drug use patterns, risk behaviors, HIV or HCV prevalence, health and social consequences, community characteristics, and public and professional perceptions. How does one decide what interventions are needed in a given setting?

Assessment of the local situation and identification of needs, followed by monitoring and evaluation, is essential for providing effective responses. Assessment should cover the following areas:

- Epidemiological situation and trends (problem drug use prevalence, user profiles, patterns of drug use, routes of administration, mortality and morbidity including HIV/HCV prevalence and incidence, risk groups and behaviors, other health and social problems, drug-related crime)
- Response situation (existence of enabling policy environment including coordination strategies and support for harm reduction, services available including criminal justice settings, service policies and practices, geographical coverage, referral pathways, service uptake and utilization, client profiles, services provided)
- Needs assessment (coverage of target populations, gaps in responses, unmet needs, contextual risk factors, barriers to services, professional and community perceptions, drug users' perceptions, engagement of stake holders)
- Recommendations (priorities for action, policy environment development, coordination needs and mechanisms, service development and delivery targets, outcome targets, key indicators for monitoring)

Conducting an assessment involves a combination of methods which can include prevalence estimation, key indicators based on administrative or service data, surveys, ethnographic research, and key informant interviews with professionals, community members, and drug users, including through the internet.

Monitoring should cover trends in the epidemiological situation based on public health surveillance and other key indicators of problem drug use and related harms, as well as trends in service provision, uptake, and utilization based on surveys or routine data from services. There are many aspects of evaluation that are useful including process, outcome, and cost-effectiveness.

Differences between settings often imply different priorities and configurations for local responses. Selected aspects of harm reduction policy in practice are discussed below.

84.2.9 Enabling Environments

Harm reduction is about fostering protective "enabling environments" as well as improving services for individuals. This involves seeking to minimize negative dimensions of risk settings while developing alternative approaches that enable safer and healthier environments for both drug users and the local community.

Early examples of local harm reduction policies are the responses of European cities such as Frankfurt, Liverpool, or Zurich to heroin epidemics and public drug scenes in the 1980s. In Frankfurt, a significant heroin market developed in the city center, attracting drug users from the city and surrounding region. Initial policy was based on strong police intervention and coercive drug free treatment, set within the wider context of a repressive and stigmatizing national policy including strict restrictions on methadone and syringe availability. This policy had the effect of chasing the drug scene around the city. Not only did it fail to solve the problem of public drug use, but it created even riskier conditions for drug injecting, and HIV and overdoses increased. Pressure for an alternative approach led to the adoption of a harm reduction policy, "To live with drug addicts," coordinated through weekly meetings of all key actors and supported by a newly created drug policy division within the municipal council (Hartnoll and Hedrich 1996). In addition to developing a wide network of harm reduction, treatment, and rehabilitation services, the policy aimed to involve public discourse on stigma and marginalization and to promote possibilities for social reintegration. While the police did not renounce responsibility for maintaining public order, they largely stopped confiscating syringes and took part in consultations over strategies to reduce the public drug scene and influx of drug users from neighboring cities. Despite continuing tensions, over time the policy environment shifted significantly, public drug use diminished, and overdoses and new cases of HIV declined.

In this case, the drive for policy change was bottom up and arose from a realization at local level, including the police and public prosecutor, that the prevailing policy was creating social environments that heightened both individual

and community harms. However, it was also important that national policy subsequently changed to include harm reduction as a major pillar of drug policy, including OST, NSPs, DCRs, and increased discretion for public prosecutors over possession of small amounts of drugs for personal use.

More recently, the importance of nurturing enabling environments has been stressed in studies of HIV among people who inject drugs in high-risk environments (Rhodes 2009; Degenhardt et al. 2010; Jolley et al. 2012).

84.2.10 Epidemiological Settings

Scaling up coverage of OST and NSPs to contain the spread of HIV and HCV is recommended in research reports (Tilson et al. 2006; Mehta et al. 2011; Grebely and Dore 2011), drug strategies (e.g., EU drug strategies since 2004), and public health policy guidelines (ECDC and EMCDDA 2011; WHO et al. 2013). What this implies in practice is situation dependent. Some studies have used modelling techniques to project the impact of different levels of coverage in different scenarios (Vickerman et al. 2007, 2012). While this approach has limitations and important margins of uncertainty surround projections, they do support several general conclusions.

The impact of different levels of coverage on incidence and prevalence of HIV and HCV is affected by baseline seroprevalence levels in risk populations as well as by individual and collective patterns of injecting risk behavior (Vickerman and Hickman 2010). Scaling up can have an important impact on containing or reducing HIV incidence and prevalence. However, since HCV transmission probability is much higher than that for HIV, higher levels of coverage and larger changes in risk behavior are needed to make an impact on HCV than HIV. Significant reductions in HIV transmission can be achieved by targeting high-risk drug injectors, while targeting low-risk users brings relatively little additional benefit in terms of HIV prevalence. For HCV, however, failure to cover lower-risk users considerably reduces the potential impact of interventions, so all drug injectors should be covered. In Britain, modelling studies suggest that early scaling up of OST and NSP helped to contain the prevalence of hepatitis C among people who inject drugs to 40 % instead of a projected 65 % that would have occurred without high coverage (Vickerman et al. 2012). In situations where HCV prevalence is already high, long-term reductions in the prevalence of chronic hepatitis C are likely to be modest and require long-term sustained coverage. To achieve large reductions in HCV incidence, it is necessary to target all injecting drug users, to reduce sharing to very low levels, and to reach them within 12 months or so of starting to inject (Vickerman et al. 2007).

In situations with low OST and NSP coverage, which globally is under 20 % in most countries (Mathers et al. 2010), it makes sense to prioritize scaling up of OST and NSPs. This also means relaxing restrictions on syringe distribution and implementing measures to increase recruitment and retention in OST. In situations where high levels of coverage of drug injecting populations have already been

achieved (e.g., 50 % or more), it may not be cost-effective to attempt to increase coverage further. For example, in countries such as the UK, it is estimated that coverage of both interventions would have to increase to 80 % or more in order to halve HCV prevalence over 20 years. It would be very difficult to achieve and sustain such a high level (Vickerman et al. 2012). Additional measures, such as treatment for HCV, may in the longer term have a significant preventive effect (Martin et al. 2011).

84.2.11 Prison Settings

Implementing harm reduction in prison raises particular challenges (see also ▶ Chap. 70, "Treatment in Criminal Justice Settings"). There is tension between the abstinence orientation of penal institutions and harm reduction approaches. Prisons are seen as institutions for punishment for illegal behavior, so interventions such as providing syringes can provoke strong opposition. Prison health services are often part of the prison administration and tend to be detached from community health care. Since security is a priority, service provision for prisoners may be seen as less pressing. As a result, health and other services for prisoners lag behind those for the general population. Further, prison administrations may be reluctant to admit that drug use, same-sex activities, and rape take place. Lack of equivalence of care between prison and community is an important barrier to improving prison-based responses to drug users and others.

Particular health risks in prison compared to the community include higher proportions of problem drug users and levels of comorbidity (psychiatric, HIV, HCV, TB), settings that encourage riskier injecting behavior when it occurs (as well as higher sex-related risks), interruptions to treatment, and post-release risk of overdose deaths.

Experience shows that it is possible to establish harm reduction interventions in a wide range of prison settings. Prison OST is both feasible and effective and has been implemented in all but a handful of European countries, though coverage varies (Hedrich et al. 2012). Equivalence of OST provision between prison and community has been achieved in some countries like the UK and Spain. In others the gap between offer and need is closing, but in some remains substantial (EMCDDA 2012b). Prison NSPs are less common, but have been successfully implemented in prisons in at least nine countries (Obradovic 2012). Evidence of impact is based on descriptive studies showing reductions in risky injecting and sharing (Dolan et al. 2003; Stöver and Nelles 2003; WHO 2007). Modalities of distribution vary and include dispensing machines (which deliver clean syringes when a used one is inserted), prison medical staff, external health workers, and trained peers (WHO 2007). Experience shows that prison NSPs do not lead to increased injecting, that syringes are not used as weapons against staff or other prisoners, that disposal is uncomplicated, and that confidentiality increases participation. Distribution of bleach to disinfect needles and syringes has been suggested, but this is an unsatisfactory alternative, especially in prison settings (Small et al. 2005). Distribution of

condoms and lubricants is feasible and contributes to reduced risk behaviors in prison (WHO 2007). All harm reduction measures in prison need support from officials, prison governors, and prison guards; otherwise interventions will be undermined, for example, by increased searches and confiscation of materials.

Continuity of care (e.g., OST or ART) between community and prison following arrest and incarceration and between prison and community following release is an important means of reducing possible harms such as relapse, disruption of infectious disease treatment, or overdose. This requires establishing clear protocols for throughcare-procedures between community and prison services.

In conclusion, it is feasible to implement harm reduction in prison settings with benefits similar to those seen in community settings. Integration of prison health care into health care for general population facilitates moves towards equivalence of care.

84.2.12 Law Enforcement Settings

Substantial numbers of problem drug users come into contact with the police. Conversely, drug-related issues can take up a significant proportion of police time and resources. Although law enforcement and health policies are not often closely related, drug use is a field where there is considerable overlap and where both sectors can benefit from partnerships that foster mutual understanding and cooperation regarding reducing harms. Examples include support by police for OST (usually because of crime reduction) and agreements over community policing with regard to syringe distribution programs, the role of DCRs in reducing public nuisance, or the status of participants in peer-based outreach. In addition to these agreements, harm reduction interventions in law enforcement settings can include drug overdose prevention, referral schemes, health interventions in police stations, and diversion into treatment (Monaghan and Bewley-Taylor 2013).

Regarding overdoses, fear of police attendance can deter those present from calling emergency services (Pollini et al. 2006). In Vancouver, police procedures were changed so that they no longer responded routinely to overdose ambulance calls, but only attended if requested by ambulance personnel (Thomas 2005). Some US states have passed "good Samaritan laws" that provide immunity from drug possession charges for overdose victims and witnesses who call emergency services in good faith to save a life. A few have implemented programs to train police officers to administer Naloxone (Monaghan and Bewley-Taylor 2013). In Britain, some police authorities have issued directives that police personnel treat drug swallowing following arrest as a medical emergency that requires immediate hospitalization (Monaghan and Bewley-Taylor 2013). Warnings of contaminated drugs detected in the local drug scene may also be valuable if the information is disseminated through acceptable peer-recognized channels.

Drug referral schemes involve specialized workers based in police stations to assess, counsel, and refer drug users to treatment. Data from a national monitoring program in Britain showed that half of those who voluntarily asked for assistance at arrest had never been in treatment (Sondhi et al. 2002), though uptake and retention

rates following referral are variable. Subsequently, drug intervention programs became more directive, involving testing and assessment orders, and rates of treatment entry and retention improved. Apart from formal referral schemes, police discretion can enable referral to local services without arrest (MacDonald et al. 2008).

Health interventions in police stations include provision of methadone or buprenorphine (by police surgeons or external doctors). In some countries this is limited to clients in OST; in others in can be administered on the basis of withdrawal symptoms. In practice many opioid users in police custody do not receive medical intervention (MacDonald et al. 2008). Some police authorities in Britain provide sterile injecting kits on release from custody (Monaghan and Bewley-Taylor 2013).

Diversion into treatment through special drug courts is widely used in the USA (US Department of Justice 2012) and some other countries. Evidence suggests that they can reduce both recidivism and court costs (Mitchell et al. 2012), but evidence of their impact on post-program drug and alcohol use, employment, social relationships, or health is scarce (Wittouck et al. 2013). There are legitimate questions over the role of coercion in harm reduction responses.

All partnerships between local health and social services and police have to overcome substantial barriers before they can operate effectively while respecting the professional responsibilities of each agency. They also have to deal with legal constraints. However, it is important to seek such partnerships, since law enforcement activities can increase the risk of harms such as infections or deaths from overdose and can conflict with harm reduction interventions such as NSPs. Arrest can increase risks, for example, through interruption of OST or ART, but it can also offer opportunities for interventions to reduce harm.

84.2.13 Overcoming Barriers

A variety of barriers can inhibit development of effective harm reduction responses. These range from legal or formal professional constraints to informal obstacles such as resistance from other services and professionals, lack of cooperation from the police, and political or community opposition. While it may be difficult at local level to change formal constraints such as laws, it is often possible to reduce resistance through active consultation and sensitivity to the interests involved.

Barriers also discourage drug users from contacting services. These include administrative barriers (registration procedures, appointments, waiting lists), fear of arrest or of children being taken into care, perceptions that services are unfriendly or cannot be trusted, lack of health insurance or costs of treatment, low accessibility due to location or opening hours, and need to contact multiple agencies for different services at different sites. It is possible to minimize some of these barriers by developing strategies to improve access to and utilization of health-care services (CDC 2012a).

Aim for coordinated services that reduce the need for repeated registration at different services. Where possible, offer multiple services at the same site to reduce the need for referral to other services. Review the geographical distribution and

opening hours of contact points and services in consultation with users. Above all, implement user-oriented policies that explicitly enshrine confidentiality and users' rights to care, and strive to create a sympathetic and supportive service.

84.2.14 Promoting Health and Equality of Care

It is essential that practitioners understand the reasons for barriers to help seeking and the primacy of confidentiality and trust. Quality of services is as important as quantity. Commitment to equality of care and basic human rights does matter (Jürgens et al. 2010).

To summarize, the principles underlying a harm reduction approach (ECDC and EMCDDA 2011) are:

- Pragmatic approach to health promotion
- Public health objectives
- Clients' rights perspective
- Based on scientific evidence and expert experience

The principles of service provision are:

- Ensure confidentiality
- Promote service accessibility
- Create a user-friendly atmosphere
- Engage in dialogue with users and promote peer involvement
- Adopt a practical approach to the provision of services
- Refrain from ideological and moral judgment
- Maintain a realistic hierarchy of goals
- Promote an enabling environment as well as caring services for clients

84.3 Conclusion

Harm reduction policies and interventions have been successfully implemented in many parts of the world. HIV among IDUs is now largely under control in countries which have implemented extensive harm reduction policies. Heroin use and related problems are largely contained in many countries where OST has reached high coverage. Other challenges include stimulants and other drugs, ageing populations of dependent users, hepatitis C, and continuing sexual transmission of infections. Harm reduction strategies will need to adapt to changing priorities.

Almost all the evidence presented in this chapter (and also ▶ Chap. 83, "Harm Reduction Interventions") comes from Europe, the USA, Canada, or Australia. Many challenges for the future lie in other regions such as Central and Eastern Asia, Central and South America, and Africa (Mathers et al. 2010; Strathdee and Stockman 2010; Stoicescu 2012). We believe that the lessons learned so far can be adapted and applied to a wide range of settings.

Over the past two decades, political and professional opinions, as reflected in resolutions and policy documents of institutions and bodies at international,

regional, and national level, have increasingly promoted a "comprehensive approach" that includes harm reduction as a central pillar. A more general trend towards viewing health and social policies on illegal drugs, infectious diseases, alcohol, tobacco, and other issues like obesity, high-risk youth, or crime prevention under a much wider umbrella also pushes towards a broader, multi-level paradigm of risk reduction and health promotion.

Discussions continue on whether harm reduction is oppositional or complementary to drug-free approaches. It is not easy to integrate abstinence-oriented and public health and safety paradigms, nor is it simple to achieve a balance between individual and community needs. However, there is clearly space, within the hierarchy of goals of harm reduction, to encourage moves away from drug use and from dependence on services for those who are able while also providing compassionate, long-term care for those who cannot. At the same time, it is important to implement policies and interventions that protect the health and well-being of communities affected by problematic patterns of drug use.

Apart from skills in dealing with individual clients, practitioners need an understanding of the social, community, and public health settings within which drug use and drug-related harms arise, as well as an awareness of how social responses can have unintended consequences. A willingness and ability to cooperate within a local network of agencies and listen to the concerns of drug users themselves is essential. This all involves a broad vision of drug use, harms, and responses and a willingness to think outside of traditional individual psychiatric and social work casework paradigms.

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Good Practice and Quality Standards

85

Marica Ferri and Paul Griffiths

Contents

Abstract

The present chapter is aimed at enabling the readers to master the methods to ascertain whether an evidence-based recommendation is appropriate for real-world patients in specific contexts. Nowadays it is crucial to develop an individual capacity for critical assessment and to know where to search for updated and reliable sources of evidence. The methods, the processes, and the practical meaning of the most popular tools for the promotion of quality are presented with links to current projects and free of cost resources for professionals. The ultimate goal of the evidence-based medicine is to provide the patients with the best possible interventions. To reach this goal, knowledge has to be translated into practice. Guidelines and standards are popular instruments to disseminate and implement evidence-based recommendations. Nevertheless to implement them into specific contexts, some decisions are needed. The chapter includes a description of the main approaches used to adapt or adopt guidelines and standards.

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Quality is never an accident. It is always the result of intelligent effort. There must be the will to produce a superior thing.

John Ruskin

85.1 Introduction

The promotion of quality and the exchange of good practice are recognized as an important strategy both to improve the effectiveness of drug-related interventions and to ensure the efficient use of limited resources. Guidelines and standards in particular are among the most frequently used tools for the promotion of quality through the translation of knowledge into the daily practice of treatment of drug addiction. But it is not always needed to publish new guidelines and standards; often the existing good quality guiding documents can be adapted to suit a specific national or local context. New disciplines have emerged focusing on methods for successful knowledge transfer to action, such as implementation science, translational science, and knowledge mobilization. A common recommendation is that the only way to a successful implementation is the promotion of participation among all the stakeholders, starting with the medical doctors and the health professionals and including the decisions makers, the patients and their families, and the public in general.

It is therefore important that the professionals in the treatment of drug addiction are familiar with the terminology and the methods of the quality promotion as these are increasingly part of their daily activity.

The contents of the evidence base change rapidly as soon as new studies are conducted and contribute with new results. This is why it is important to master the methods to ascertain whether a recommendation is appropriate for real-world patients in specific contexts. It becomes crucial to develop an individual capacity for critical assessment and to know where to search for updated and reliable sources of evidence.

To this purpose the present contribution was conceived. The evolution from evidence base to implementation is described giving some details about the terminology and references for further reading. The methods, the processes, and the practical meaning of the most popular tools for the promotion of quality are also presented with links to current projects and free of cost resources for professionals. In particular it is explained how time and resources can be saved by *adapting* or *adopting* already published evidence-based guidelines to specific needs and contexts. The current initiatives for the development of quality standards in drug addiction treatment at international and at national level are described and compared, and for each of them, the links for free downloading of documents are included. To complement the information on implementation, we included a description and references to some recent initiatives in the medical field in which the participation of drug addiction treatment professionals is crucial but still not sufficient. In fact all those initiatives are studying strategies to effectively communicate with decision makers and patients. In a conclusive part, two examples of use of standards are compared more in depth, in one case as part of an accreditation system and in another as a support for implementation and measuring of quality criteria.

85.2 From Knowledge to Implementation

85.2.1 Knowledge Translation into Practice: From Evidence to Change

The overall aim of good practice sharing and standards development is the achievement of improvement in the quality of treatment. Clearly quality is not an abstract concept but rather an umbrella definition for series of measurable achievements in the health and well-being of the treated patients.

"*Primum non nocere*" – first of all do not harm – the phrase attributed to the Hippocratic Oath, reminds that the first aim of a health intervention is to avoid harm.

And it is exactly with this intention that the pioneers of the evidence-based medicine called the attention on the discrepancies between research results and medical practice, which would have cost human lives (Cochrane 1999). According to their claims the timely application to practice of the results from clinical research would have saved many lives and reduced subsequent costs to the society (Egger and Smith 1997). For example, randomized controlled trials proving the effectiveness of systemic glucocorticosteroids administered to pregnant women at risk of preterm delivery to reduce respiratory distress syndrome in newborn babies were available already in the 1970s, but it took almost 20 years before this intervention became a common practice (Roberts and Dalziel 2006).

The possible effect of the delay in the adoption of this practice was that a significant number of premature babies probably suffered and possibly died and needed more expensive treatment than was necessary (Rennick 2006).

The movement for the systematic collection of scientific results for dissemination outside the restricted circles of researchers and academics became known worldwide at the beginning of the 1990s (Sackett et al. 1996) and was boosted by the foundation of the Cochrane Collaboration, an international organization aimed at helping "healthcare providers, policy-makers, patients, their advocates and carers, make well-informed decisions about health care, by preparing, updating, and promoting the accessibility of Cochrane Reviews" (Chalmers and Glasziou 2004).

In 1998 an editorial group specifically devoted to drugs and alcohol was founded with its base in Rome (Davoli and Ferri 2000), and since then around 70 reviews on the various interventions (including prevention) for drug and alcohol problems were published and updated.

The availability of good quality research on effectiveness of treatment for drug problems has dramatically increased over the last years, even though important gaps still remain to be bridged with evidence (Turner and McLellan 2009). The availability of studies and of systematic reviews nurtured the production of clinical guidelines as a major tool for the dissemination and application of evidence in practice.

For example, a recent survey for the identification of treatment guidelines in Europe identified more than 140 sets of guidelines for the treatment of drug addiction (EMCDDA 2011). Nevertheless the practical effects of such a massive effort to produce clinical guidelines were not clear. When measured, the impact on quality of treatment seemed not impressive. Some surveys performed in the medical

field, not specifically in the drug addiction one, showed that clinical guidelines are applied to practice in only 50–70 % of day-to-day decisions, and the main reason given for not applying them is that they are of limited relevance to patients and healthcare staff (Parchman et al. 2011). Moreover, in a recent debate promoted by the British Medical Journal about the effectiveness of guidelines (Grol and Wensing 2004), it was pointed out that to ensure clinical guidelines have an impact on actual care and practice, activities beyond the mere production and dissemination should be instigated (Ferri and Bo 2012).

This type of considerations along with the need to reduce cost and improve quality and outcomes must be at the base of the evolution towards the *knowledge translation into practice* approach (Brownson et al. 2012). In fact, moving from the concept of evidence to that of knowledge expands an idea already present in the definition of evidence-based medicine. The practice of evidence-based medicine integrates clinical expertise with the best available evidence from systematic research, explained David Sackett (1996). "Without clinical expertise, practice risks becoming tyrannised by evidence, for even excellent external evidence may be inapplicable to or inappropriate for an individual patient" reinforced then. Probably "knowledge" is a better term to put together evidence with expertise. *Knowledge translation* has been defined as a "dynamic and iterative process that includes the synthesis, dissemination, exchange and ethically sound application of knowledge to improve health, provide more effective health services and products, and strengthen the health care system" (Canadian Institutes of Health Research 2012). Knowledge translation is not the only term that has been used to name this tendency towards practical use of knowledge to improve practice. According to Straus and colleagues (2009), more than 90 terms were identified in the literature. According to them, in Europe, preferences are for "implementation science" or "research utilization," whereas the terms "dissemination and diffusion," "research use," and "knowledge transfer and uptake" are more frequently preferred in the United States. The Canadian "knowledge translation" has been adapted by others, including the United States National Center for Dissemination of Disability Research and the World Health Organization (WHO).

The lowest common denominator among the above described different terms is a move beyond dissemination of knowledge into actual use of it to transform practice. "Knowledge creation (i.e., primary research), knowledge distillation (i.e., the creation of systematic reviews and guidelines) and knowledge dissemination (i.e., appearances in journals and presentations) are not enough on their own to ensure the use of knowledge in decision-making" (Straus et al. 2009).

A definition of the "best-practice" concept was recently developed by a group of European experts convened by the EMCDDA. In brief, best practice is the best application of the available evidence to current activities in the drugs field. A number of factors were identified as contributing to making an intervention qualify as "best practice." In summary, a best-practice intervention is based on the most robust scientific evidence available regarding what is known to be effective in producing successful outcomes, and it is tailored to the needs of those it addresses. Methods used will be transparent, reliable, and transferable and can be

updated as the knowledge base develops. With regard to implementation, local contextual factors will be taken into account, and the intervention will be harmonized with other actions as a part of a comprehensive approach to drug problems. Best practice is closely linked to the concept of "evidence-based practice," and it requires the careful integration of both scientific knowledge and implementation expertise in order to appropriately adapt the intervention to the single individual and/or to a specific context. A best-practice intervention should provide better outcomes than other interventions and therefore also allow a rational allocation of resources (Ferri and Bo 2012).

There remain challenges associated with the promotion of best practice through guidelines, standards, and other similar tools. The first is to make sure that they are based on reliable scientific evidence and that they are regularly updated when new systematic reviews are published. The second is to make best use of the currently existing guidelines. Finally, it is important to ensure that guidelines and standards are appropriately implemented.

85.2.2 Quality of Interventions: The Main Tools and Their Life Cycle

Clinical guidelines are the main instrument to disseminate evidence-based interventions via recommendations for practice that are based on a clear methodology for the appraisal, synthesis, and grading of the available evidence (Connis et al. 2000). Evidence-based guidelines are produced by convening multidisciplinary groups of experts who systematically assess the quality of the available evidence and classify the recommendations according to the level of supporting evidence. The level of evidence is determined by a synthesis of relevant studies' design (systematic reviews), number of participants studied, and the number of studies sharing the same results along with the overall measure of effect found by pooling the results of the studies. Each recommendation should have an indication of its strength, which clarifies how and when this is applicable to the patients. Although the level of evidence influences the strength of a recommendation, there are conditions under which, even where there is a lack of evidence from studies, the appointed group of experts may attribute a high strength to some recommendations. This is the case for some interventions, such as hydration for hospital patients or blankets to prevent heat loss in trauma patients, that are supported by practical experience and do not need to be based on experimental evidence. Guidelines may therefore include a statement such as "we recommend that this intervention is offered to most patients, even though there are no studies which prove or refute the effects, and this recommendation is based only on expert opinion." In some milestone manuals for guidelines development, these are indicated as *good practice points* (SIGN 2011).

Another example is where patients cannot be directly studied for ethical reasons (such as exposing newborn babies to different drug therapies). In such cases, the recommendations can be based on the results of studies on other types of patients. In practical terms, this system, which separates level of evidence from

strength of recommendations, produces two separate – but not completely independent – scores. In general, evidence-based guidelines are published by independent organizations that are able to assemble experts who are free from conflicts of interest and who represent different fields and professions. These groups generally involve as many stakeholders as necessary to ensure they appropriately address all the different aspects of a question, including patients' preferences and practical concerns arising from the experience of the carers (EMCDDA 2011).

In 2000, a collaboration was established of people interested in addressing the shortcomings of the grading systems used in guideline development, "the grading of recommendations assessment, development, and evaluation" (GRADE) working group (Guyatt et al. 2011). Over the years, this group has developed and continuously updated a common, sensible, and transparent approach to grading the quality of evidence and the strength of recommendations. This system has been adopted by several international organizations among which the EMCDDA (the Best Practice Portal); the World Health Organization; Agency for Healthcare Research and Quality (AHRQ), United States;and the National Institute for Clinical Excellence in the United Kingdom.

The evidence-based clinical guidelines are meant to facilitate the application of updated evidence to practice, and therefore, they are supposed to be timely revised. An indication of a specific date for revision should be stated clearly, and the choice of this date should be based on an assessment of the time in which new evidence is likely to be available.

This anticipation of a date for the availability of new evidence is in general possible because evidence-based clinical guidelines are based on systematic reviews of studies. These are identified through structured "search strategies" developed on the basis of a list of "clinical questions" that the guidelines should address. On the basis of those questions – which should be relevant to the patients and detailed enough to allow the appropriate search for the available evidence (Schardt et al. 2007) – the methodologists search, identify, and select a number of systematic reviews of evidence. The latter are based on published and unpublished studies and should also identify – in ad hoc created registries (WHO 2013) – the ongoing studies. Those registries collect information from the very beginning of the clinical studies and follow up each step until the publication. The entity (or the individual researcher) registering a clinical trial is requested to include a date of completion. Although these dates can be changed during the study period, they provide an idea when new results can be available.

A number of tools have been developed to assess the quality dimensions in guidelines, the most recent being the "appraisal of guidelines for research and evaluation" (AGREE Collaboration 2003), which was created to address the issue of variability in guideline quality by assessing methodological rigor and transparency. The updated version, "AGREE II" (AGREE Next Steps Consortium 2009), is composed of six domains aimed at assessing whether or not the scope and purpose of the guidelines is clearly indicated; the stakeholders' involvement is sufficient to represent the views of the intended users; the process of development was rigorous; the presentation and text are clear; and the guidelines are fit for purpose and free from conflicts of interest.

Several are nowadays the international inventories of guidelines from all over the world which can be consulted freely to find relevant documents. Among those, the more important are the inventory maintained by the Guidelines International Network (http://www.g-i-n.net/library) containing over 6,000 sets of guidelines for evidence-based healthcare (in multiple languages) and the National Guidelines Clearinghouse (http://www.guideline.gov/), an initiative of the Agency for Healthcare Research and Quality (AHRQ) in the United States, which publishes guidelines from any countries provided they are in English. The website of the National Guidelines Clearinghouse offers an automated function to compare different guidelines upon their main characteristics and to obtain synthesis of guidelines. The main aim of the inventories of guidelines is to avoid duplication of efforts making good quality guidelines available for adoption or adaptation in different contexts.

85.2.2.1 Adaptation of Guidelines to Everyday Practice Under Local Circumstances

Clinical guidelines can be elaborated and published at several levels: international, national, or local level. The World Health Organization and the United Nation Office on Drugs and Crime, for example, published guidelines and principles on the treatment of drug addiction (WHO 2009) (Table 85.1).

Being a very resource-intensive activity, guidelines are in general commissioned to specialized national agencies which have the capacity for convening a number of stakeholders from all the involved parts and reduce the risks of conflicts of interest. Examples of agencies to develop clinical guidelines are the National Institute for Clinical Excellence in the United Kingdom; the Scottish Intercollegiate Guidelines Network; the Finnish STAKES, National Research and Development Centre for Welfare and Health; the French National Health Authority (HAS); the New Zealand Guideline Group (went in voluntary liquidation in 2012); the Canadian Task Force on Preventive Health Care; and many others. An indicative list of organizations which develop and publish guidelines is available in the website of the Guidelines International Network (GIN 2012).

Guidelines which are published at general level may require some further elaboration before they can be effectively applied to the everyday practice. The translation of evidence-based recommendations into practice is the so called "implementation" process.

The implementation activities can follow two general approaches mainly depending from the "distance" between the context where the guidelines were issued and that where they have to be implemented. In some cases it is sufficient to *adopt* the guidelines through the development protocols at service level in which the guidelines' recommendations are broken down into actions and responsibilities, agreed by the healthcare personnel. This type of protocols (which can be also called *clinical pathways*) supplement clinical recommendations with hospital (or service)-specific details and, in some cases, can emend those recommendations which are considered not fitting with the local context (Groot et al. 2008). These

Table 85.1 Recently published quality standards in the treatment of drug addiction

Title and year of publication	Supporting organization	Target groups	Structure of the standards	Web address
European Minimum Quality Standards (EQUS) 2012	European commission	Professionals performing interventions, service directors and managers responsible for the functioning of their institutions and staff, and health authorities, planners, and policy makers who are mainly concerned with the drug demand reduction activities at the system and network level	Structural standards of services Process standards at the service level Process standards of interventions Outcome standards at the system level	www.isgf.ch
Proposed continental minimum quality standards for treatment of drug dependence 2012	African Union	Unspecified	14 principles of effective drug dependence treatment 15 standards for treatment of drug dependence and 3 standards for evaluation and assessment	http://www.au.int/en/
Principles of drug dependence treatment 2008	UNODC WHO	Unspecified	9 principles: Description and justification Components Actions to promote each principle	http://www.who.int/substance_abuse/publications/principles_drug_dependence_treatment.pdf

National standards				
Service delivery for people with coexisting mental health and addiction 2010	New Zealand Ministry of Health	This guidance document is aimed at all those who have an interest and responsibility for planning, funding and providing mental health and addiction services including District Health Boards, Non-governmental organisations and the Ministry of Health. The content will be of interest to staff working in services, consumers and service users, carers and others who have contact with these services.	General principles Tips for mental health and addiction planners and funders Tips for mental health and addiction service managers and clinical leaders Suggested actions for local planning	http://www.health.govt.nz/publication/service-delivery-people-co-existing-mental-health-and-addiction-problems-integrated-solutions-2010
Principles of drug addiction treatment 2012	NIDA USA	Unspecified	13 principles of effective treatment 22 frequently asked questions	http://www.drugabuse.gov/publications/term/33/Guidelines%20and%20Manuals
Alcohol dependence and harmful alcohol use quality standard 2011	National Institute for Clinical Excellence (UK)	The public, health and social care professionals, commissioners, and service providers	13 statements and 13 quality measures for: Structure Process Outcome	http://publications.nice.org.uk/alcohol-dependence-and-harmful-alcohol-use-quality-standard-qs11/list-of-statements
Quality standard for drug use disorders 2012	National Institute for Clinical Excellence (UK)	The public, health and social care professionals, commissioners, and service providers	10 statements and quality measures for: Structure Process Outcome	http://publications.nice.org.uk/quality-standard-for-drug-use-disorders-qs23

(*continued*)

Table 85.1 (continued)

Title and year of publication	Supporting organization	Target groups	Structure of the standards	Web address
Quality framework for mental health services in Ireland 2005	Mental Health Commission Ireland	Service users as well as the different nature and scale of organizations involved in service delivery	8 themes 24 standards 163 criteria	http://www.mhcirl.ie/Standards_Quality_Assurance/Quality_Framework.pdf
Standards for integrated care pathways for mental health December 2007	NHS quality improvement Scotland	Local management, health staff at service level	9 process standards 21 care assessment, planning, delivery and outcome standards 16 condition-specific standards (only one relevant to drug addiction) 2 service improvement standards	http://www.healthcareimprovementscotland.org/programmes/mental_health/icps_for_mental_health/standards_for_integrated_care.aspx

protocols can be disseminated in the realm of some peer-led educational activities; and they can include reminders and other initiatives aimed at reinforcing the application of recommendations in practice (Burgers et al. 2003).

In other cases an *adaptation* process is put in place, where the source guidelines are further analyzed by a group of local experts who draft new contextual-wise recommendations. Customizing clinical practice guidelines to a particular context and involving local stakeholders and the end users of the guideline in this process has been identified as a way to improve acceptance and adherence (Harrison et al. 2010). In general, but not necessarily, the *adaptation* occurs when (inter) national guidelines are to be applied at local level. In this case the adaptation process can be kept into consideration more than one set of guidelines and imply a process similar to the one needed for drafting a new guideline. The major difference lies on the search for source documents that in the case of an *adaptation* focus on guidelines rather than on systematic reviews of evidence (and or primary studies) as in the case of a development of a new guideline.

ADAPTE (www.Adapte.org) is an international organization of methodologists researchers, guideline developers, and guideline implementers who aim to promote the development and use of clinical practice guidelines through the adaptation of existing guidelines. The organization created a resource toolkit that can be freely downloaded in the Guidelines International Network website (www.g-i-n.net).

Quality standards are becoming an increasingly popular tool for ensuring quality of interventions in healthcare. In general terms standards are principles and sets of rules about what to do and what to have (Brunsson and Jacobsson 2000) presented as voluntary to a number of potential adopters. According to one of the most known organization for standards development, a standard is a document, established by consensus and approved by a recognized body, that provides, for common and repeated use, rules, guidelines, or characteristics for activities or their results, aimed at the achievement of the optimum degree of order in a given context (ISO 2004; ISO 2004). Typically the standards proposed in the health field refer to content issues, to processes, or to structural (formal) aspects of quality assurance, such as environment and staffing composition.

Quality standards can be developed by private sector organizations as it is the case for the International Standards Organization (ISO 2013); national private, nonprofit organizations like the American National Standards Institute (ANSI); the Association Française de Normalisations (AFNOR); and the British Standards Institute (BSI). The great majority of these organizations have been founded at the beginning of the twentieth century and some after the Second World War. Standards can also be developed by international governmental organizations like the United Nations, the Organization for Economic Co-operation and Development, and the European Union. In fact standards are a good way to propose harmonization especially by those organizations whose members are sovereign states that cannot be obliged to follow some rules (Brunsson and Jacobsson 2000). Nevertheless there are also several national organizations especially in the health field which develop quality standards. In the case of these organizations, quality standards are intended as sets of rules based on evidence used to implement the interventions

recommended in clinical guidelines. The standards which are developed by the National Institute of Clinical Evidence in the United Kingdom, for example, are typically composed of a general statement and a measure which can be used to assess the quality of care or service provision specified in the statement. "The quality statements are clear, measurable and concise and describe high-priority areas for quality improvement. They are aspirational (they describe high-quality care or service provision) but achievable" (NICE 2012).

Several international organizations are undertaking standards development for health interventions in the drug demand reduction.

The European Commission financed a study on the Development of an European Union Framework for minimum quality standards and benchmarks in drug demand reduction (EQUS), proposing a set of 22 quality standards for treatment (the study included also 33 standards for prevention and 16 for harm reduction).

According to the background paper of this project, in the medical sciences, quality standards are determined by different stakeholders: health authorities, insurance companies, service providers, professionals, and patients. Each of these professional categories brings different goals, interests, and priorities which need to be reflected in the standards in the light of the underlying scientific evidence. The project, whose lead investigator was Ambros Uchtenaghen (Uchtenhagen and Schaub 2011), divided the quality standards into four dimensions:

1. *Structural quality*, e.g., standards relating to the physical environment, staff, training, etc;
2. *Process quality* standards relating to the process of an intervention, e.g., diagnostic assessment;
3. *Outcome quality and economic quality*, e.g., standards to measure the cost-benefit ratio.

The *structural standards for services* cover areas like the physical accessibility of treatment services (which need to be located in places easily reached by public transport) or the environment where the treatment take place which should be adequate (to allow privacy during consultations) and safe. Another important aspect is the need for a documented diagnosis as a basis for treatment choice. Staff education and composition is also mentioned in terms of ensuring the presence of medical and nursing staff along with psychologists or social workers and multidisciplinarity with at least three professions represented.

The *process standards at the service level* included the assessment of substance use history, diagnosis, and treatment history along with the somatic and the social status for each patient including an assessment of the psychiatric conditions.

Each patient should be provided information on the treatment options available and should be provided a treatment plan tailored on his/her individual needs.

Treatment plans, assessments, changes, unexpected events, and any relevant information should be recorded and kept confidential. Each treatment service should promote cooperation with other agencies and services to ensure an appropriate response to the needs of their patients (whenever a service is not equipped to deal with all needs of a given patient, an appropriate other service is at hand for referral) and should ensure continuous education for the staff members.

The *outcome standards proposed at the system level* included the goals of health and social stabilization of patients and the reduction of illegal or non-prescribed psychotropic substances. Monitoring included the level of utilization (each service should provide information on the number of slots or bed utilized) and the ratio of discharges occurred as planned or for different reasons.

Internal and external evaluation of services was also proposed as a standard.

Beyond the list of proposed standards, the project-added value lies on the process adopted to consult the stakeholders and to identify several levels of standards. Namely, the stakeholders were interviewed by rounds of Internet-based consultations about the level of implementation status and acceptability of the proposed standards in their respective countries. Through this strategy it was possible to identify a long list of standards and grade them by priority of implementation. In fact, the EQUS study also included a review, involving experts from 24 European countries, of existing quality standards already implemented at the national level. With regard to drug treatment processes, the standards most frequently reported as already implemented were in the areas of client data confidentiality and assessment of clients' drug use history, whereas the standards concerned with routine cooperation with other services, and those focusing on continuous staff training, were less often implemented. In the area of treatment outcomes, the two types of standard most frequently reported as implemented were those with goals linked to health improvement and reduced substance use. Among the standards less likely to be applied were those focusing on external evaluation and monitoring client discharge; problems related to the implementation of these standards were reported.

This approach may allow the participating countries to set their own goals and to pace the achievement of them on the basis of their own capacity and priority. This process would also be greatly facilitated by the existence of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), a decentralized agency whose aim is to provide sound and comparable information on drugs in Europe. Thanks to its impartiality and comprehensiveness of information, EMCDDA can support the countries volunteering for the adoption of the quality standards in setting their goals and measuring their successes.

The European standards have not been formally adopted yet, but the EQUS study represents the beginning of an ongoing process to reach consensus over a minimum set of quality standards in drug demand reduction.

Another initiative at supranational level was undertaken by the African Union which has recently proposed a list of Continental Minimum Standards for treatment of drug dependence as a guide to member states (African Union 2012). In the introduction of these standards, there is a synthesis of the current situation of drug consumption in Africa stating that "the levels of drug consumption continue to grow in Africa while there is a tendency toward stabilisation in North America and Europe"; therefore, "an in-depth revision of current drug policies has become necessary (in Africa) in view of the increasing human and social costs and threats to democratic institutions."

Table 85.2 Processes for guidelines adaptation at local level

Document	Process	Professionals involvement	Output	Definition
Guidelines (national or international)	Adoption	Service personnel	Service protocol/ clinical pathway	A comprehensive set of rigid criteria outlining the management steps for a single clinical condition or aspects of organisation (http://www.openclinical.org/guidelines.html#gandp)
Guidelines	Adaptation	Stakeholders	Locally adapted guidelines	The local adaptation of national guidelines has been proposed as a way of increasing the benefit of local ownership, while maintaining scientific validity (Khunti and Lakhani 1998)

The text supports that "provisions should be made towards treatment of drug users which was instrumental in stabilising drug consumption in the West," while "The criminalisation and marginalisation of drug users has increased drug-related health problems and contravened universal fundamental human rights." In summary those standards are presented as an application of the lessons learned in a different context to change a particular situation. This intention captures the exact spirit of sharing of good practice. A general description of recent initiatives of standards for the treatment of drug addiction is reported in Table 85.2, and some of them will be deeply explored.

In general terms it can be observed that the existing standards (at their different level of implementation) seem to be triggered by several reasons: the harmonization of the existing services, the translation in practice of the evidence-based guidelines, the consistency between policy decisions and service provision, and the need to measure the results of interventions. These reasons are diversely reflected in the mentioned initiatives mainly in relation with the level where the standards are proposed. The life cycle of quality standards depends on the supporting evidence, but not completely. In fact when it comes to human rights or general safety measures, the relevant principles are imperishable.

Clinical pathways are structured, multidisciplinary plans of care designed to support the implementation of clinical guidelines and protocols. In a recent past it was considered that this definition was variedly interpreted by different stakeholders until a recent systematic review (Kinsman et al. 2010) clarified the concept.

The clinical pathways are essential to the translation of evidence-based guidelines at service level. They are in fact meant to "detail essential steps in care of patients with a specific clinical problem" and sequence "the actions of a multidisciplinary team" (De Bleser et al. 2006). In clarifying which actions should be undertaken to practice evidence-based recommendations, clinical pathways "facilitate translation of national guidelines into local protocols" (Campbell et al. 1998) and allow continuous improvement by monitoring and evaluating variances.

Clinical pathways are commonly adopted in the United States where in 2003 it was reported that almost 80 % of the hospitals used this tool (Kinsman et al. 2010). Evidence supports the adoption of clinical pathways at hospital level for the reduction of in-hospital complications (such as infections, bleeding, and pneumonia), improved documentation, and possibly a reduction in the length of stay (Rotter et al. 2010). An experience of integrated clinical pathways in mental health has been reported in Scotland where the National Health Service (NHS) Scotland is taking a national approach to improving the quality and safety of mental health services. The program started with the publication of national standards by NHS Quality Improvement Scotland (NHS QIS), setting out the framework for development at local level.

The emphasis of development and implementation of the ICPs lies with local NHS boards to ensure they are developed with local ownership and to meet the needs of the local population. However, to ensure accreditation by NHS QIS, the local ICPs must incorporate the national standards and evidence improvement to the quality of care provided (El-Ghorr 2010). In Belgium there is the European Association for the development of clinical pathways (http://www.e-p-a.org/about-epa/index.html. Among the objectives of this organization, there is the setup of an international network for pooling know-how on clinical pathways and the promotion and fostering of international cooperation between healthcare researchers, managers, and healthcare providers from European countries and the wider international community. The association has a journal which publishes research results on the development of clinical pathways.

85.2.3 Participation: A Key for Successful Implementation

There are two main elements underlying all the instruments for quality improvement mentioned in the previous paragraphs (evidence-based clinical guidelines, quality standards, and clinical pathways). These two elements are the evidence base and the stakeholders consensus. The last three decades have been devoted to define and share a valid methodology for the identification assessment and synthesis of the available evidence. This activity successfully brought to a general understanding about the terminology and the sources of correct information. Nowadays the role of evidence to base decisions is widely recognized, and the access to good quality sources of evidence is increasingly available.

The new challenge seems to lie on the promotion of an authentic participatory implementation of evidence-based interventions.

The same pioneers of the evidence-based medicine are now exploring strategies to communicating and involving two crucial stakeholders: the decisions makers and the patients (this latter category includes also family members, civil society organizations, community representatives (Deber et al. 2005)). Projects like SUPPORT financed by the European Commission's 6th Framework Programme (Lavis 2009) and the most recent DECIDE (Treweek et al. 2013) co-funded by the European Commission under the Seventh Framework Programme are both aimed at supporting decision makers in the use of evidence.

SUPPORT targets policy makers as a diverse group that includes cabinet members (e.g., Ministers of Health or Finance), elected officials (e.g., chairs of legislative committees), senior civil servants (e.g., directors of primary healthcare programs), and high-level political appointees (e.g., heads of government agencies). In spite of being aware of the differences that can exist among the countries due to the different political systems, the leading project managers of SUPPORT state that what all the decision makers have in common is the authority to take or influence decisions directly. The project encompasses several tools for boosting evidence-based decision making in various settings including low- and middle-income countries and high-income countries. As the other mentioned project, DECIDE, also SUPPORT, sought strategies for the involvement of public in evidence-based decision making (Oxman et al. 2009). In particular DECIDE, whose target is Europe, is composed of eight work packages, three of which devoted to identify best strategies to communicate with specific target groups such as health professionals, policy makers and managers, and patients and public.

The two projects have similar objectives though following different approaches: DECIDE focuses on guidelines and recommendations, while SUPPORT aimed to support policy-relevant reviews and trials. DECIDE on the other hand is developing tools that will help policy makers to make a decision about, say, whether to pay for a particular healthcare innovation in their region. Additionally, it is developing tools to make understanding the research information that forms the basis for guideline recommendations easier for a wide audience, including policy makers and the public. To some extent, DECIDE builds on the work of SUPPORT.

Even though these projects are important, quite often the exercise of knowledge translation brings to the appreciation of huge gaps in knowledge, gaps that are difficult to fill with methods for gathering consensus and taking decisions in the lack of evidence. The only possible way forward to fill those gaps is to propose new studies to find answers. These new studies should rely on mixed methods to get sound evidence from several sources and, of course, to be based on the priorities of the end users of the answers they should provide, such as the patients (Liberati 2011). In the United Kingdom, Sir Iain Chalmers, one of the founders of the Cochrane Collaboration, has undertaken a new initiative for the proactive involvement of patients in the setting of research priorities through the James Lind Alliance initiative (Petit-Zeman S FAU – Cowan and Cowan). The James Lind Alliance brings together patients, carers, and clinicians to identify and prioritize the uncertainties, or "unanswered questions," about the effects of treatments that they agree are most important and makes the list of research questions public and available for researchers and research funders. Not always the area of addiction is represented in these initiatives. The main linkages are granted by the Cochrane Group on Drugs and Alcohol and by the European Monitoring Centre for Drugs and Drug Addiction which are working in partnership to bring the typical problems of this field in the broader perspective of knowledge translation.

Some of the characteristics of the drug addiction field can be shared by other medical conditions. For example, the behavioral component calls for research that cannot be only based on experimental studies. Important aspect of knowledge can

be in fact found on long-term observational studies, and in some cases they require qualitative analysis which is more difficult to be systematically retrieved with the typical search strategies adopted in systematic reviews and even more difficult to be assessed for quality and included in meta-analysis (Gough 2012). Nevertheless there are some added values in the drug addiction field which compensate for those extra efforts. The impact of interventions on public health and security makes drug addiction an important point on every political agenda and need to be based on the best available evidence.

85.2.4 Examples of Frameworks for Quality Standards

Several evidence-based guidelines are currently available for the treatment of drug addiction, in particular for the combined pharmacological and psychological approaches for opioid dependence, and these guidelines are issued at international and national level. Differently, the publication of quality standards for drug addiction treatment is less common, as the majority of the existing standards in drug addiction refer to prevention (UNODC 2013; EMCDDA 2012). Following we will describe two examples of standards for drug addiction treatment at national level, in European countries, namely, in the Czech Republic and in the United Kingdom.

In Czech Republic the implementation of quality standards for treatment of drug addiction dates back to 1995 for initiative of the Interdepartmental National Drug Commission (now Government Council for Drug Policy Coordination). Called minimal standards, these were adopted by the Association of Non-Governmental Organizations (ANO) for Addiction Prevention and Treatment for evaluating the quality of member organizations and newly established facilities. After further elaboration occurred in the subsequent 4 years, those standards became the basis for a certification process, which recognizes that a specific service provider is in line with predefined quality standards. Since 2004 the adherence to quality standards is assessed by specifically trained external evaluators. The current process for the certification of treatment providers was kicked off in 2005, and it included a transition period to allow the treatment provider services to start the certification process. After that period, certification became a prerequisite for applying for state grant programs. The overall aim of the certification process was the improvement of the quality of the network of services including a cost-effective administration of public funds. The certification process brought to the integration of the drug addiction services into the medical and social national system.

The underlying principles are as follows: voluntariness, certification is not required to provide drug services but only to apply for public funds; transparency, the evaluation process is carried out according to published criteria; and objectivity, the actual evaluation of quality is performed by an independent agency who appoints trained evaluators and the facility providers can point out any possible conflict of interest.

The standards are at the base of certification and accreditation process. The core activity of the certification process includes that a group of trained assessors visits the service providers to collect relevant information. Active participants in this

process are the facilities requesting the certificate of quality (those wishing to apply for public funds); the Certification Agency (an independent institution that arranges on-site examinations, communication between the parties of the certification process, and training of certificators); the certification team carrying out on-site examinations (composed by at least three trained certificators); the Certification Board of the Government Council for Drug Policy Coordination (deciding about certification request results and validity of certification ranging from 1 to 4 years); and the Executive Board of the Government Council for Drug Policy Coordination – to which the facilities can address their complaints about, for example, the composition of the certification team. In fact, before the certification can start, the agency and the requesting facility have to agree on the date and the composition of the team of assessors. Subsequently a number of previously identified employees and clients are interviewed with semi-structured questionnaires. The on-site examination in general lasts one day at the end of which the team of assessors drafts a report with a proposal for certification or suggestions for improvement. The report is shared with the interested facility which is given the opportunity to comment in writing.

The report is therefore completed and forwarded by the Certification Agency to the Certification Board of the Government Council for Drug Policy for the final decision.

Overall the process takes around 2 months, and the facilities requesting certification have 15 days to contest the results.

In the United Kingdom the National Institute for Clinical Excellence (NICE) publishes evidence-based clinical guidelines for many different medical disciplines including drug addiction. Sets of quality standards are derived from the best available evidence such as NICE guidance and other evidence sources accredited. They are developed in collaboration with NHS and social care professionals, their partners, and service users. The standards consider issues like evidence of effectiveness and cost-effectiveness, people's experience, safety, equality, and cost impact. The quality standards are considered central to supporting the government's vision for an NHS and social care system focused on delivering the best possible outcomes for people who use services (Health and Social Care Act 2012). This act clarifies that the Secretary of State "must have regard to the quality standards prepared by NICE." The care system should consider those standards in planning and delivering services to secure continuous improvement in quality. NICE quality standards do not provide service specifications but rather define priority areas for quality improvement. Nevertheless those standards are the basis to ensure that the providers of health and adult social care in England meet the standards of quality and safety required to by the Care Quality Commission.

The standards developed by NICE are typically composed of a general statement complemented by a measure. These quality measures are drafted only after the quality statement wording has been agreed and addresses the structure of care or services, process of care or service provision, and, if appropriate, outcome of care or service provision. The majority of measures refer to process and are expressed as a numerator and denominator to define a proportion in which the numerator is

a subset of the denominator population. For example, for the standard "People who inject drugs have access to needle and syringe programmes in accordance with NICE guidance," there is a measure at the structure level, which is "Evidence of local arrangements to ensure people who inject drugs have access to needle and syringe programmes in accordance with NICE guidance," complemented by a measure of outcome: (a) proportion of people who inject drugs who access needle and syringe programs, wherein the numerator is the number of people who access needle and syringe programs and the denominator is the estimated prevalence of injecting drug users, and (b) incidence of blood-borne viruses among people who inject drugs.

To clarify the implications of the standard, a breakdown of meanings of the standard for each stakeholder is included: service providers ensure systems are in place for people who inject drugs to have access to needle and syringe programs in accordance with NICE guidance; needle and syringe program staff ensure people who inject drugs have access to needle and syringe programs in accordance with NICE guidance; commissioners ensure they commission services for people who inject drugs to have access to needle and syringe programs in accordance with NICE guidance; and people who inject drugs have access to needle and syringe programs that are nearby, have suitable opening hours, and provide injecting equipment and advice on reducing the risk of harm. The standards include also that the sources of data should be considered in the measurement. Furthermore, at NICE there is an implementation team to support key audiences and organizations to maximize the uptake of guidance and quality standards. The team assesses the aids and barriers to implementation and provides practical support tools for commissioning, service improvement and audit, education, and learning. The team prepares reports on the uptake of guidance that are used to inform the development of the quality standard. The implementation team collaborates with national bodies and local organizations, through local implementation consultants, to support the use of quality standards and to facilitate shared learning. Overall the process to produce standards at the National Institute for Clinical Excellence lasts indicatively for 42 weeks.

These two examples suggest the possibility of different approaches to the use of quality standards. In the Czech experience in fact, the development of the standards represents an initial effort, whereas the actual focus seems to lie on the certification and accreditation process including several levels of training and a "learning by experience" process. Furthermore, the entire experience initiated around 20 years ago has been conceived and developed specifically in the treatment of drug addiction.

On the other hand the National Institute for Clinical Evidence has created along with the Department of Health and other key partners a core library of topics for quality standard development in health-related topics, among which alcohol dependence and drug use were included. In this case the focus seems to be on the development itself of the standards which *translate the evidence-based guidelines* into general statements and measures of outcomes at the system level including the indication of the sources of data to be used for the assessment of the implementation. Furthermore, NICE offers the support of an implementation team to enhance local adoption initiatives.

85.3 Conclusion

Quality of intervention is entrenched to evidence base, and in the last 20 years, important progress has been made in the availability of good quality systematic reviews of effectiveness in the field of drug addiction treatment. Nevertheless important gaps in knowledge still exist and need to be addressed by further investment in research. To ensure that research answers concrete problems arising from the daily experience of those affected by the drug problems at several level, it is crucial that the end users of research results – such as practitioners, patients, and decision makers – are involved in the selection of priority for investigation.

Currently the attention seems to be focused on how to better communicate evidence to policy makers, patients, and the general public. It is clear that the achievement and maintenance of quality in the treatment of drug addiction need the participation of all the stakeholders. The agencies which provide the data needed to assess the current situation and set the future goals, the organizations producing evidence-based documents, the decision makers at service provider level, and those managing the local, regional, and national level have to collaborate with the practitioners, to offer the best possible treatment to the drug users. The drugs users, the families, and the public have to proactively be involved in any decision and should be able to speak out their needs and problems.

The tools to translate evidence into quality of treatment have to be understandable by all the relevant stakeholders to empower them in a reiterative process of testing and lessons learned.

Quality is a continuous process where each new achievement has to be seen as a step towards new goals.

Glossary of Terms

Accreditation is the process by which an institution delivering a service is independently assessed for quality against some predefined criteria. Accreditation requires a set of minimum standards, which are set by the accrediting body.

Benchmarking is the process of comparing service processes and performance metrics to best practices from other services. Dimensions typically measured are quality, time, and cost.

Clinical pathways are structured, multidisciplinary plans of care designed to support the implementation of clinical guidelines and protocols.

Guidance is a general term that covers documents such as guidelines and quality standards.

Guidelines are "statements that include recommendations intended to optimise patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options" (Institute of Medicine 2011). They are designed to assist carers' and clients' decisions about appropriate interventions in specific circumstances.

Protocols, in general, are documents that specify the procedures to follow to perform some tasks, typically those used to conduct a study or to implement some guidelines at individual service level.

Standards and quality standards are principles and sets of rules based on evidence (Brunsson and Jacobsson 2000), used to implement the interventions recommended in guidelines. They can refer to content issues, to processes, or to structural (formal) aspects of quality assurance, such as environment and staffing composition. In some cases, standards are legally binding.

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Ethical and Legal Aspects of Interventions in Addiction Treatment

86

Ambros Uchtenhagen

Contents

Abstract

The UN conventions present the international legal framework; they urge member states to provide treatment and rehabilitation but prohibit consumption and possession of scheduled drugs. This creates problems for providing treatment and harm reduction programs to patients who are not or not yet ready to stop illicit drug use. Other international documents, notably from the World Health Organization and the United Nations Office on Drugs and Crime, are strongly in favor of agonist substitution treatment and harm reduction measures. Within this framework, national legislation has much room for diverse preferences; the International Narcotic Control Board regularly comments the national practices, as well as the European Monitoring Centre for Drugs and Drug Addiction for the EU member states. An international trend gradually prefers therapeutic measures over criminal sanctions for drug users.

The international ethical framework is set by the universal declaration and European convention on human rights, striking a balance between individual rights and societal interests. Less ambiguous guidance comes from medical ethics claiming the full range of patient's rights for addicted persons.

Note: Some of the material is based on earlier work of the author about ethical aspects of treatment and care in addiction (Uchtenhagen & Guggenbühl 2000; Uchtenhagen et al. 2005; Uchtenhagen 2010a, b).

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The respective conduct codes for medical professions are regional or national and include procedures how to deal with ethical conflicts. Conflicting situations frequently occur, e.g., around the principles of autonomy or of confidentiality.

An essential ethical element of treatment is its effectiveness and avoidance of harm, asking for scientific evaluation of therapeutic approaches, services, and systems. The ethical acceptability of agonist substitution treatment and of harm reduction measures is based on rigorous evidence of their effectiveness. Other aspects concern the limits of social acceptability of addictive behavior and the limits of what can be attained for an individual patient by therapeutic interventions; avoidance of harm often is the more immediate objective than full recovery. In a public health perspective, effects at population level rather than at individual level are a priority, aiming at good coverage of treatment needs by good accessibility and affordability of services.

86.1 Introduction

Addiction treatment is historically and until present guided by the basic understanding of addictive behavior. Interventions are shaped accordingly to prevailing paradigms explaining substance use and substance dependence. Legislation is a preferred instrument to limit consumption and addictive behavior, through preventive interventions as well as sanctions. The development of liberal societies caring for individual freedom and responsibility, less interference with lifestyles and personal choices, and the need for ethical standards in human behavior came to the forefront and resulted in various rules guiding interventions and therapist's conduct. This process in the area of addiction treatment has been taken at hand, but with persisting differences in orientation and a need for conflict management.

86.2 International Frameworks and National Diversities

86.2.1 Legal Aspects

86.2.1.1 The International Framework: The UN Conventions

The UN conventions of 1961, 1971, and 1988 have some implications for delivering addiction treatment.

The Single Convention urges "to take all practicable measures for the prevention of abuse of drugs and for the early identification, treatment, education, after-care, rehabilitation, and social reintegration of the persons involved." While this article 38 does not indicate how treatment should be delivered, Resolution II declares that "one of the most effective methods of treatment for addiction is treatment in a hospital institution having a drug free atmosphere," and urges the provision of such facilities (UN 1961).

The Convention on Psychotropic Substances of 1971 (UN 1971) restricts the "use and possession of, substances in Schedules II, III and IV to medical and

scientific purposes," thereby criminalizing patients in treatment who continue sporadically or regularly to use illicit drugs (schedules II, III, and IV include drugs such as barbiturates, benzodiazepines, and buprenorphine). Art. 7 states for schedule I drugs to "prohibit all use except for scientific and very limited medical purposes by duly authorized persons." What the limitations are is open to interpretation. Art. 9 requires "that substances in Schedules II, III and IV be supplied or dispensed for use by individuals pursuant to medical prescription only, except when individuals may lawfully obtain, use, dispense or administer such substances in the duly authorized exercise of therapeutic or scientific functions." Licensed pharmacists however may "supply, at their discretion and without prescription, for use for medical purposes by individuals in exceptional cases, small quantities, within limits to be defined by the Parties, of substances in Schedules III and IV." Art. 20 urges to "take all practicable measures for the prevention of abuse of psychotropic substances and for the early identification, treatment, education, after-care, rehabilitation and social reintegration of the persons involved." Also, treatment may be provided either as an alternative to conviction or punishment or, in addition to punishment, if abusers of psychotropic substances have committed such offences (Art.22).

In the 1988 Convention (UN 1988), preparatory acts for personal use of scheduled substances are criminal offences (Art. 3,2):

> Subject to its constitutional principles and the basic concepts of its legal system, each Party shall adopt such measures as may be necessary to establish as a criminal offence under its domestic law, when committed intentionally, the possession, purchase or cultivation of narcotic drugs or psychotropic substances for personal consumption contrary to the provisions of the 1961 Convention, the 1961 Convention as amended or the 1971 Convention

Implicitly, this includes criminalization of use (no use without preparatory acts).

The International Narcotic Control Board (INCB) was set up in 1968, with the main task to control and facilitate the implementation of the Single Convention at national level. The following conventions have revised and restated the functions of the Board.

In summary, the UN conventions urge the treatment and rehabilitation of drug abusers but prohibit the consumption of narcotics and psychotropic substances (including tranquilizers and sedatives), which creates problems for patients in treatment (continued use is often a reason to exclude patients from treatment) and even more problems for harm reduction approaches designed to diminish the medical risks of substance use (for persons in addiction treatment and outside of treatment). Agonist maintenance treatment is viewed critically by INCB as a potential source of diversion of narcotics to the illegal market (INCB 2011). However, the conventions allow diversion to treatment as an alternative to punishment.

86.2.1.2 Other International Frameworks

Some international documents are mentioned here with relevance to addiction treatment and specifically in regard to agonist maintenance treatment and harm reduction interventions. These evidence-based documents present strong recommendations which are not legally binding.

The World Health Organization (WHO) and the United Nations Office on Crime and Drugs (UNODC) published Principles of Drug Dependence Treatment in 2008. This discussion paper is in strong support of agonist maintenance treatment for opioid dependence: "Opioid agonist pharmacotherapy is one of the most effective treatment options for opioid dependence when methadone or buprenorphine are administered at an individualized dosage for a period of several months to years." The discussion paper also urges to implement legal frameworks which guarantee protection from potential sanctions for those seeking treatment (WHO/UNODC 2008).

The UNODC, WHO, and UNAIDS "Technical Guide for countries to set targets for universal access to HIV prevention, treatment and care for injecting drug users," published in 2009, has a range of preventive measures (e.g., needle and syringe exchange programs) among its recommendations, thereby complementing the treatment recommendations (UNODC/WHO/UNAIDS 2009).

In Europe, the EU Action Plan 2005–2008 (EU 2005) foresaw harm reduction measures as a specific action for the implementation of Objective 14 (prevention of health risks related to drug use) and Objective 15 (availability and access to harm reduction services). The implementation process and the available evidence on outcomes is presented in a monograph (Rhodes and Hedrich 2010).

86.2.1.3 Diversity of National Legislation

At the national level, narcotic laws and policy guidelines mirror a diversity of principles, priorities, and preferences, even when countries have ratified the UN conventions. Treatment of substance abuse is one of the essential elements, but how it is defined, for whom it is available, under which circumstances, and which approaches are officially accepted are all subject to major differences. One example is the national guidelines for substitution treatments of opiate dependence; an analysis of 28 national guidelines found a large variety of indication criteria and practices (Uchtenhagen et al. 2005).

An official source of information on problems with the implementation of the UN conventions is presented in the annual reports of the International Narcotic Control Board (INCB). The 2011 report includes, e.g., information on unacceptable treatment problems, such as diversion of prescribed pain medications or allowing safe injection rooms (INCB 2011, p. 38). The setting up of the lack of aftercare is admonished (p. 59). On the other hand, large compulsory treatment centers are mentioned (p. 78), as well as detoxification, rehabilitation, and counseling services (p. 83); opiate substitution treatment (p. 51, 78); and needle/syringe exchange programs (p. 51), without indicating their acceptability and outcomes.

A complete and updated collection of national drug laws and drug policies is presented by the European Monitoring Centre on Drugs and Drug Abuse (EMCDDA); it includes not only the EU member states but also acceding and candidate countries as well as neighboring and Central Asian countries (EMCDDA 2012). The same source provides a systematic information on treatment approaches and harm reduction approaches in these countries.

86.2.1.4 Sanctions

Use and possession of illegal drugs for personal use are prohibited in a range of countries. For Europe, an analysis of national practices is presented (EMCDDA 2009). Only rarely, prison sentences are handed out in case of infraction. In other regions, imprisonment and compulsory treatment are more common, e.g., in labor camps (WHO 2009).

In some countries, drug possession is an offence which may entail imprisonment or even capital punishment. A systematic overview is not available. In Islamic law, use of any drugs including alcohol is prohibited and sanctioned, but it also provides care of those suffering from medical conditions.

Agonist maintenance therapy is prohibited in Russia (MHR 1995), while a growing number of countries supports and expands this approach, replacing criminal sanctions.

86.2.2 Ethical Aspects

86.2.2.1 Ethical Basis of Interventions: Human Rights

The Universal Declaration of Human Rights (UN 1948) contains a number of relevant conditions, such as no discrimination (art.2), no degrading or inhuman treatment (art.5), and right of equal access to medical care and social services (art.25/1), but also that everyone has duties to the community (art.29/1) and that limitations of rights and freedom are admissible on the basis of "just requirements of morality, public order and the general welfare" (art.29/2).

In view of conflicts this may create, a recent initiative proposes the formulation of meta-rules providing guidance on how to resolve conflicts in human rights (Arosemena 2013).

The European Convention on Human Rights (Council of Europe 1950) further stipulates that a person's liberty may be deprived in case of lawful detention of alcoholics or drug addicts (art.5/1/e), with a right to appeal to a court (art.5/4).

In summary, these statements try to establish a balance between protecting the individual rights of the person and respecting the needs of society for public order, general welfare, and even morality. There is large room for interpretation, so that every society can decide on the compatibility of addictive behavior with the nature and extent of the abovementioned requirements. Compulsory measures against persons with substance dependence may be admissible on the basis of national laws.

86.2.2.2 Ethical Basis of Interventions: Medical Ethics

Medical ethics apply only if and inasmuch as substance dependence is understood as a medical condition. This has been the official position of the leading medical organizations since decades (and brain research has identified it as a "brain disease," thereby giving it a biological basis) (Leshner 1997). The substance-dependent person is a patient and should enjoy the status and all the rights of patients.

The current medical science defines substance dependence as a condition with diagnostic criteria, described in the generally acknowledged diagnostic systems International Classification of Diseases ICD-10 of World Health Organization (WHO 2010) and Diagnostic-Statistical Manual of Mental Disorders DSM-IV TR of the American Psychiatric Association (APA 2000). New editions of both systems are in preparation. The criteria include biological symptoms (tolerance, withdrawal symptoms in case of discontinued use), psychological symptoms (craving, desire to reduce consumption), and behavioral symptoms (loss of control over consumption, consuming in spite of perceived negative consequences).

ICD-10 includes a diagnosis of harmful use (with negative health consequences of use), while DSM-IV includes a diagnosis of abuse. These conditions are also considered to be a medical condition inviting therapeutic interventions.

What are the consequences for the treatment of addiction? Examples of the general conduct codes are the Standards of Conduct of the American Medical Association (AMA 2001) and the Good Medical Practice of the English General Medical Council (GMC 2006). Main issues are the patient's autonomy of decision, informed consent, dignity and confidentiality, nondiscriminatory beneficence, and non-maleficence, but also keeping up professional standards by continued education and networking with other services and colleagues in order to provide the best possible care. In addition, the American recommendations include a responsibility to seek change in official or legal requirements which are contrary to the best interests of the patient. These codes usually acknowledge the occurrence of ethical conflicts and provide links for support in such cases.

In the absence of specific rules for the treatment of substance dependence, the general ethical rules for good medical practice apply. The four major principles are as follows: do no harm, improve the well-being, respect the autonomy, and apply justice. It is obvious that even these few principles cannot be followed without creating conflict (Rust 2000).

Involuntary intervention to prevent harm is in conflict with the autonomy of an unwilling patient. Treating all patients as being equal (principle of justice) is impossible where the resources are limited. Also, confidentiality and data protection often are in conflict with administrative and law enforcement interests in case of illicit drug use. All such conflicts must be carefully examined, in the best interest of all concerned. When the patient's interests collide with those of relatives or other third parties, a common solution must be found to the extent possible. It is advisable to recur to an ethical concilium if major consequences are expected from the decision. The principle of respecting the autonomy of the patient must never be overruled in the name of some abstract societal value without the presence of concrete harm implications for others.

86.2.2.3 Ethical Justification of Interventions

Human rights as well as medical ethics mention the interests of society which may be in conflict with the interests of the individual. In fact, the ethical justification to interfere with a person's substance use or dependence resides in negative societal consequences. In the case of substance dependence, treatment is justified in order to

avoid such negative consequences. Among the appropriate measures are all treatments which help to bring a majority of addicts into treatment, without disregarding their autonomy, and to optimize accessibility of treatment services. In the case of hazardous and harmful use, treatment by early and short interventions (e.g., motivational interviewing) can have positive effects.

As in other medical fields, therapeutic interventions are justifiable if efficient and effective. This principle is part of what is named "consequential ethics," in contrast to dogmatic ethics which call for complying with a given norm whatever the consequences may be.

Substance use is a factor in many social and cultural events, as a facilitator of social contact and a source of emotional well-being but also of destructive or aggressive behavior. The acceptable limits of intoxication and behavior, of substances used and of opportunities for consumption, are cultural specific and are to be respected when dealing with substance dependence (Edwards and Arif 1980). For instance, a major difference between western and Asian cultures is the place of the individual within the family system; while the individual's interests and autonomy are a core concept of most western psychotherapies, the integrity and the interests of the family are the higher value in many Asian societies.

In a paternalistic attitude, substance-dependent persons must be protected against wasting their personal resources and potential achievements. However, such an attitude collides with the present position that interference is only justified on the basis of negative consequences of a person's behavior for others. Also, many people have lived or live a productive life in spite of their substance dependence, and to interfere with their lifestyle would cause more ethical concerns than to respect their autonomy.

Developing one's own resources and shaping one's own life is to be facilitated by education and by societal organization, but it is ultimately in the responsibility of the person itself. Conditional are the freedom of choice – and the freedom of the will. Is addiction leaving any room for choices, is it a negation of free will and therefore the basis for involuntary intervention? This has been debated extensively. At present and on the basis of research evidence, we have a more differentiated view. The decision of many to change their lifestyle and go to treatment (Ekendahl 2007; Bergmark 2008) or to stop the dependence without professional support (the so-called self-healers) (Klingemann and Sobell 2007) demonstrates the ability of many addicts to make a choice and stick to it.

This notion is reinforced by observations of regaining consumption control by former addicts (Kaya et al. 2004) and that not the substance alone but also the personality and the social environment had a role in the development of dependence and that many users keep their consumption under control or regain control under more favorable conditions (Zinberg 1984; Robins 1993).

A basic ambivalence – substance dependence as a medical condition or a moral weakness – is reflected in the opposition of medical and moral treatment. Moral treatment is understood to be educational and admonishing. The medical approach is to help the addict in getting motivated for change by appropriate empathy and information, while confrontation and reproaches risk to reinforce the resistance

against any change. It is important to give the patient the feeling that he is taking the decisions and doing the necessary steps forward himself. Special methods have been developed for enhancing the motivation for change, and they have become an important element in today's treatment of alcohol and other drug problems (Moyer et al. 2002; Gossop 2006).

In summary, treatment of substance dependence is expected to help the individual to make his own choices and to regain self-responsibility, rather than to make the decisions for him.

86.2.2.4 The Goals of Treatment: A Hierarchy of Objectives

The goals to be reached through treatments of substance dependence (and which therefore are the criteria for measuring outcome in treatment evaluation research) have changed over the last decades. While the goal of abstinence was traditionally on top of the list, the present situation can be summarized as follows: the primary goal is the patient's survival, moving to health improvements (or at least prevention of deterioration), to improvements in social integration, to reductions in substance use (moving away from addictive behavior), to improvements in quality of life (as defined subjectively by the patient), and ultimately resulting in a responsible and satisfactory lifestyle. Abstinence is not always needed for reaching these objectives, nor does abstinence guarantee to reach them.

A national example of listing the objectives is given in the report on Models of Care by the UK Department of Health (Department of Health 2002):

- Reduction of psychological, social, and other problems directly related to drug use
- Reduction of psychological, social, or other problems not directly attributable to drug use
- Reduction of harmful or risky behaviors associated with the use of drugs (e.g., sharing injecting equipment)
- Attainment of controlled, nondependent, or non-problematic drug use
- Abstinence from main problem drugs
- Abstinence from all drugs

This document fully endorses the principle of consequential ethics in prioritizing the reduction of the various forms of drug-related harm, including social, medical, legal, and financial problems, until the drug-dependent patient is ready and able to come off drugs.

86.2.2.5 Cure or Care?

Treatment is often identified with cure (in the sense of healing an illness), while care means serving a chronic patient without chances for healing. As such, care is an equivalent to harm reduction, meaning all interventions designed to improve the health and social status of a chronic addict who continues a dependent behavior (harm reduction is more than HIV prevention). The present debate on treatment and harm reduction is often a debate on opposing principles of action which cannot be reconciled. In this debate, harm reduction has been disqualified as an approach to prolong dependence, to make substance use acceptable for young people, and to

undermine the readiness of addicts for treatment. A recent movement to promote recovery as a complete resocialization without drugs disqualifies agonist maintenance treatment which is only accepted as "maintenance to abstinence."

Today, in the light of the updated treatment objectives, harm reduction is considered an ally rather than an opponent of treatment. Accordingly, the treatment system must be an integrated system that enables abstinence and harm reduction services to work together, in order to provide a continuum of care, including:

- Easily accessible low threshold services that meet the immediate needs of continuing drug users
- Clear processes for motivating users to move away from drug-dependent lifestyles
- Clear processes for referring users into structured treatment programmes that promote stabilization or abstinence (quoted from Stevens et al. 2006, p. 6)

86.2.2.6 Tailoring Treatment to Individual Needs

Bearing in mind the diversity of etiology, symptoms, and stages of substance dependence, it becomes obvious that treatment cannot be uniform for all dependent persons. In addition, treatment needs in different age groups and other target groups (gender, ethnicity, comorbidity, etc.) may differ considerably as well. Treatment must respond to the specific needs of an individual patient, on the basis of a comprehensive needs assessment and a treatment planning process where patient and therapist work together on a shared understanding of what is needed and what should be done.

This concept of a needs-based treatment has been intensively researched. I mention two large studies from USA: the National Treatment Improvement Evaluation Study (NTIES) documented the results of needs-based treatment planning and found a significant correlation between 1-year outcomes (measured as drug-free urines) and the number of needs included in the treatment plan (Gerstein et al. 1997). A comparison of basic, average, and enhanced services for heroin dependence evidenced better retention and outcomes in services where psychiatric and social care was available to patients (McLellan et al. 1997). In both studies, covering the needs for psychiatric care and living conditions (housing, jobs) was found to be especially important. This again has consequences for the hierarchy of objectives: a reduction of substance use is facilitated by improved living conditions and not necessarily their precondition. "Matching treatment settings, interventions, and services to an individual's particular problems and needs is critical to his or her ultimate success in returning to productive functioning in the family, workplace, and society" is therefore one of the principles of addiction treatment (NIDA 2012).

86.2.2.7 Public Health Interventions Versus Individual Care

Coverage of treatment needs: Reaching the majority of drug injectors became a primary objective in order to slow down the HIV epidemic. The public health priority is to offer treatment to all persons in need of treatment. Individual care is optimized by high-quality treatment, but public health cannot accept high-quality standards for a few as long as the many are not reached adequately. This principle

includes a monitoring of the treatment needs in a given population and, accordingly, a careful planning of the treatment system as a whole. The responsibilities – ethically and professionally – are well distributed: medical practitioners are responsible for good individual care, service directors are responsible for good practice in their services, and health authorities are responsible for good coverage of treatment needs.

Cost-effectiveness of interventions: When caring for the treatment system as a whole, the next step is to take the responsibility for making best use of the available human and financial resources for treatment. This means to look at how much effective treatment is provided at what costs. It does not suffice to give a priority to treatments with good evidence for effectiveness but to treatments which provide effectiveness at the lowest costs in terms of staff and budget. A recent approach are efforts which intend to make best use of resources through models of stepped care, matching patients to specific treatments, on the basis of their characteristics and needs (see ▶ Chap. 82 "Stepped Care Models in Addiction Treatment" in this section).

Harm reduction: An efficient protection of public health goes beyond providing treatment for substance-dependent persons. It includes all measures which are effective in protecting the health and social status of active users, in the interest of users as well as of the population at large.

Accessibility and affordability of treatment: Neglect of patients in need of treatment can take many forms. For instance, an analysis of national guidelines for substitution treatments of opiate dependence showed a range of restrictive access criteria, such as minimal age, minimal duration of dependence, polydrug use, and lack of confidentiality, and likewise restrictive criteria for a continuation of treatment, such as persistent illicit substance use or bureaucratic limitation of treatment duration (Uchtenhagen et al. 2005). Other examples are the denial of social support and/or medical care to active alcohol or drug users or smokers. Examples are the denial of liver transplants to persons with alcohol problems, in spite of research evidence that survival rates in those who continue to drink are not lower than in other patients (Fireman and Rabkin 2001), and the denial of Hepatitis C treatment with Interferon to active drug injectors on the basis of wrongly presumed lack of compliance (Edlin et al. 2001). Excluding addiction treatment from health insurance and reserving treatment to those who can pay for it are other examples.

In summary, the ethical implications are obvious: without appropriate accessibility and affordability of treatment, there is no way to reach the "health for all" goal of good coverage and of treating all patients as equal.

Quasi-compulsory and compulsory treatment: Is it advisable to force addicts into treatment, when they are not motivated to engage in it by themselves, in view of an objective of optimal coverage? It is a common understanding that addicts do not enter treatment unless there is some external or internal force behind such a decision. The forces are quite different, ranging from health concerns to social pressure by family or employer to legal pressure in order to avoid losing the driver's license or going to prison. This is called the "continuum of coercion" (Weisner 1990). The scientific evidence on the effectiveness of such "coercion" is

contradictory (Gerdner 1998; Wild et al. 2006). A recent multi-country study on quasi-compulsory treatment (QCT, treatment on court order as an alternative to imprisonment, with the consent of the patient) documented that perceived pressure does not translate into higher motivation; no significant differences in outcome were found between QCT patients and control groups of voluntary patients (Stevens et al. 2006).

Coercion through mutually agreed consequences of substance use during treatment (contingency management) is recognized to be helpful, but more so when using positive reinforcers than sanctions (Miller and Flaherty 2000; Schumacher et al. 2007). From an ethical standpoint, it is reluctantly accepted under the term of "Ulysses coercion" (Odysseus wanted to be bound to the mast of his ship in order to resist the temptations of the sirens, Tännsjö 1999).

In summary, the findings indicate that coercion may have a role in supporting patient motivation for change, on the basis of informed consent, but it cannot replace motivation by compulsory measures without consent.

86.2.2.8 The Case of Agonist Maintenance Treatment

Rationale and origins: At first view, prescribing agonists with dependence liability to persons suffering from substance dependence seems to be paradox. One of the main arguments against agonist prescribing refers to a prolongation of dependence, considered to be unethical. How can we understand the rise and successes of this therapeutic approach (also known under the terms substitution or replacement treatment)? The main objective is to replace uncontrolled use of an addictive substance by the controlled provision of a medication acting on the same receptors as the original substance. The secondary objectives to be reached are reduction of the uncontrolled substance use, reduction of adverse health and social effects of uncontrolled use (including a reduction in drug-related delinquency), and normalization of lifestyle (including drug-free social contacts, improved housing, and employment conditions). These objectives are in line with the hierarchy outlined above. The primary objective is reached by prescribing and controlled intake of an agonist, the secondary objectives by eliminating the need to purchase the original substance of dependence and by ancillary care.

The introduction of agonist maintenance treatment is closely linked to the experience of unsuccessful detoxification and abstinence-based treatment. Maintenance without substitution was practiced in Roman times (the emperor Marc Aurel was maintained on opium by Galenus, the eminent physician), and daily dosages of opium were provided to dependent persons in Southeast Asia in the nineteenth century (Westermeyer 1982); ironically, after the ban of opium these persons switched to heroin (Westermeyer 2006). First attempts at substitution were to replace opium by alcohol in the sixteenth century (Elliott 1920), morphine by heroin (Kramer 1977), and morphine by cocaine (Freud 1884) in the nineteenth century. These attempts were far from being successful. A first well-designed and scientifically based model was developed by Dole and Nyswander: the methadone maintenance scheme (Dole and Nyswander 1965). They used oral methadone, a full opiate agonist, with a longer half-life than injected heroin (controlled intake of one

dose per day can block the heroin craving effectively). The model included ancillary care for medical and social conditions of enrolled patients.

Apart from opiate replacement, only nicotine replacement has been introduced into present medical practice, while former alcohol maintenance for alcoholics is discontinued.

Results: Methadone maintenance is one of the most frequently and best researched therapeutic approaches. Extensive reviews of the pharmacological aspects, of service delivery, and of therapeutic outcomes have been published (Arif and Westermeyer 1990; Ward et al. 1998; Uchtenhagen 2003; Farrell et al. 2004; Health Canada 2008). In addition to methadone, buprenorphine and retarded morphine have been introduced and researched as replacement medicines in the treatment of opioid dependence, with similar outcomes. The positive findings in terms of health and social improvements, including a massive reduction of delinquency, were complemented by the fact that agonist maintenance treatment has the greatest potential to bring heroin-dependent persons into contact with therapy and care. It therefore became one of the most welcome instruments for limiting the spread of blood-borne diseases – HIV/Aids and hepatitis – among drug injectors. The reduction of risky injecting behavior and of seroconversion rates in methadone patients became evidenced for community-based programs (Metzger et al. 1993) and for prison-based programs (Stallwitz and Stoever 2007). Economic evaluation documented the cost-effectiveness of methadone and buprenorphine maintenance treatment (Connock et al. 2007).

Based on the evidence, methadone and buprenorphine have been scheduled by the World Health Organization as essential medicines (WHO 2004a, b). Also, international evidence-based scientific guidelines for agonist maintenance treatments have been published (WHO 2008).

Concerns: A major concern was a weakening of the motivation to change and therefore a prolongation of addictive behavior through agonist maintenance treatment. There is no evidence for this claim. A multisite major cohort study showed a relapse rate of methadone maintenance patients to daily opiate use of only 27 % at 12 year follow-up (Marsh et al. 1990). The DATOS study from USA and the NTORS study of the UK, both multisite prospective cohort studies, found comparable outcomes at 5 year follow-up in patients who were enrolled in residential drug-free and in methadone maintenance treatment (Hubbard et al. 2003; Gossop et al. 2003).

In summary, the ethical justification of agonist maintenance treatment in the modern form was to provide otherwise treatment-resistant heroin addicts with an effective approach to improve their health and social situation without asking for total abstinence from narcotic substances.

86.2.2.9 Conflicts in Ethical and Legal Orientation

In numerous concrete situations, human rights and medical ethics are difficult or impossible to respect as well as national or local legal conditions. A number of such situations has been indicated throughout this text. Sometimes, an appropriate conflict management may help, especially if the application of an opportunity

principle is permitted. In other situations, there is no such solution. The way out is indicated by the ethical code of AMA: to engage in an effort to change laws which prove to be incompatible with responsible care for the addicts (AMA 2001).

86.2.2.10 Implications and Recommendations: A Final Statement

The essential ethical message is well summarized in the WHO international guidelines for the psychosocially assisted pharmacological treatment of opioid dependence (WHO 2008):

> When making clinical decisions for the treatment of people with opioid dependence, ethical principles should be considered, together with evidence from clinical trials; the human rights of opioid dependent individuals should always be respected. Treatment decisions should be based on standard principles of medical care ethics – providing equitable access to treatment and psychosocial support that best meets the needs of the individual patient. Treatment should respect and validate the autonomy of the individual, with patients being fully informed about the risks and benefits of treatment choices. Furthermore, programmes should create supportive environments and relationships to facilitate treatment, provide coordinated treatment of comorbid mental and physical disorders, and address relevant psychosocial factors.

There is not much to be added. The statement applies fully as the main recommendation for all treatments of substance dependence. It is a perpetual agenda for future generations.

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The UN Drug Conventions: Evidence on Effects and Impact

87

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Contents

Abstract

The three international drug treaties cover many psychoactive substances ("drugs"), although not tobacco (now under a separate treaty) or alcohol. They include a penal regime to enforce the limitation of use to medical or scientific purposes, a trade regime concerning drugs for medical use, and a planning scheme to ensure adequate supplies of medical opiates. The system, initiated in 1912, had shifted its main focus by the 1988 treaty to combating the illicit markets which accompany a prohibitory system. The place of the drug treaties in the United Nations system and the bodies which compose the system are briefly characterized. Nearly every country has signed each treaty, though often with

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reservations. The option this involves of denouncing and reacceding with reservations has now been successfully used by Bolivia concerning coca leaves. The system has assured access to pain medication in most high-income countries, but not in much of the world, where the system's emphasis on law enforcement has often indirectly but effectively cut off supplies. In terms of controlling legal medical markets, the system has had mixed success. But the system has mostly failed in cutting off the illicit drug trade. In a system which has been committed to a prohibitory approach, there are recent signs of change, particularly in the Americas, which are briefly discussed.

87.1 Introduction

The United Nations drug control system is organized around three international treaties: the Single Convention on Narcotic Drugs of 1961, as amended by a protocol of 1972; the Convention on Psychotropic Substances of 1971; and the UN Convention Against Trafficking in Narcotic Drugs and Psychotropic Substances of 1988. Their texts and the official commentaries on them are conveniently available online: https://www.unodc.org/unodc/treaties/index.html.

The treaties, of course, do not cover the whole range of psychoactive substances. There is a separate treaty on tobacco, the Framework Convention on Tobacco Control of 2003, negotiated under the auspices of the World Health Organization, and an International Convention Against Doping in Sport (many of the substances covered by it are psychoactive), adopted in 2005 under the auspices of UNESCO. Notably absent from the list of substances under international control is alcohol, although it was actually the subject of the first international drug treaty, controlling "trade spirits" in colonial Africa, negotiated in 1889 but now in abeyance (Bruun et al. 1975). The 2012 WHO Expert Committee on Drug Dependence briefly discussed whether alcohol would qualify for listing under the UN drug conventions and referred this for consideration at a future Expert Committee meeting (WHO 2012, p. 16).

From the perspective of the inherent harmfulness of different psychoactive substances (e.g., Nutt et al. 2010), what is included and what is excluded in the three "drug treaties" are not easily defensible except as reflecting the vagaries of history. But despite the ongoing convergence in scientific thinking about psychoactive substances (Courtwright 2005), it is still true that discussions of international drug control which take account of the whole range of drugs and their regulation are rare (for an exception, see Braithwaite and Drahos 2000).

In this chapter, however, attention remains focused on the three UN drug treaties. We consider the intended functions of the treaties, the institutional arrangements for their implementation, and what evidence is available on effects and impact of the system. As this is written at a moment when change in the system seems increasingly possible, a brief discussion of potential future developments is also included.

87.2 Intended Functions of the Treaties

The treaties have three main functions: as a penal regime to enforce limitation of use of scheduled substances to medical or scientific purposes, as a specialized trade treaty controlling international trade in psychoactive substances for medical use, and as a central planning scheme to ensure adequate supplies particularly of opiates for medical use.

87.2.1 A Penal Regime to Enforce Drug Prohibition

The Single Convention, as its name conveys, replaced an array of treaties and protocols which had accumulated since the first opium treaty, the Hague Convention of 1912. But the Single Convention went well beyond what was in the previous treaties, signaling a change in the system's orientation (Carstairs 2005). Whereas the prime concern of the previous treaties had been with regulating international trade in plant-derived drugs (opiates, cocaine, and cannabis), the 1961 Convention introduced requirements that possession and delivery, along with a wide variety of market-related actions concerning the drugs covered, be criminalized under a country's domestic laws (Bewley-Taylor and Jelsma 2012). What had been a system concerned primarily with controlling international movement of drugs became a system committed to enforcing prohibitions on nonmedical use of the drugs, with each country's criminal laws as means of enforcement. The international prohibition system as it now exists can thus be said to have begun with the 1961 treaty.

The 1971 treaty greatly expanded the scope of the system by including a wide range of synthetic substances, many of them with pharmaceutical uses. The market controls in the 1971 treaty are weaker than those in the 1961 treaty, reflecting the powerful influence of the pharmaceutical industry on the treaty negotiations (McAllister 1991). The requirement concerning criminalization under domestic law is more simply stated than in the 1961 treaty, requiring penalization of "any action contrary to a law or regulation adopted in pursuance of its obligations under this Convention." But since the convention requires a medical prescription to authorize use of a covered drug, any possession or use without a prescription should be criminalized.

The 1988 treaty, as its name reveals, represented a further shift in the system's focus, with more attention focused on combating the illicit markets which had emerged as a by-product of the prohibition system, including for the first time controls on precursor chemicals used in the preparation of controlled drugs. But in an effort to eliminate any remaining ambiguity, it also included a further provision on criminalization at the level of the individual drug user: that a signatory country should "establish as a criminal offence under its domestic law, when committed intentionally, the possession, purchase or cultivation of narcotic drugs or psychotropic substances for personal consumption."

The system of treaties inaugurated by the 1961 Convention, then, has as a main goal the elimination or at least suppression of any nonmedical use of drugs, aiming

to eliminate illicit markets in drugs by a five-pronged approach: (1) particularly for drugs covered by the 1961 treaty, by restriction of the supply of the drugs, limiting production to the estimated medical need for the drugs; (2) by a system of export and import permits, restricting legitimate trade in the drugs in accordance with a receiving country's wishes; (3) by requiring that most substances covered by the treaties be in a prescription system, as a way of confining availability to medical control and use; (4) by criminalizing production, sale, and other market activities outside those permitted for drugs for medical use; and (5) by criminalizing users for purchase or possession of drugs other than for medical purposes.

87.2.2 A Trading and Marketing Control Regime

The treaties also set up a trading and marketing regime, a special kind of trade treaty which aims more to structure and direct international trade, rather than the more usual main aim of trade treaties – to facilitate trade. Requiring that an import permit be issued by the receiving country before drugs can be shipped to it means that a country can control and indeed cut off the legal supply of a drug to its residents.

Although the drug treaty system was established before the formation of the current system of international trade treaties, it has served an informal function of protecting the substances under its jurisdiction from any trade disputes seeking to open up markets for controlled drugs. This contrasts with the situation for alcohol and tobacco (O'Brien 2013; Baumberg and Anderson 2008; Shaffer et al. 2005).

87.2.3 A Central Planning Scheme to Supply Medical Needs

Particularly through the 1961 treaty and its predecessors, and particularly for opiates, the international system is intended to ensure that supplies of opium-derived drugs for medical use are available globally. Each signatory country is supposed to send to the International Narcotics Control Board (INCB) annual data on medical use of opioids and estimates of requirements for the next year. There is a system of permits for countries to grow opium to meet the demand from the medicinal market (around 2010, nearly half the legal supply was grown in Tasmania). Particularly with respect to opium, the aim is a globally controlled system of cultivation, manufacture, and supply which will ensure that medical needs everywhere for opioid medications are met.

87.3 Institutional Arrangements for Implementation of the Treaties

In the United Nations system, the drug treaties come under the jurisdiction of the UN's Economic and Social Council (ECOSOC), which serves as the final deciding body for issues such as the scheduling of drugs under the treaties and determines

whether a conference should be called to consider amendments to the treaties. The political body governing the drug system is the Commission on Narcotic Drugs, with 53 member states elected by ECOSOC but with proceedings open to attendance by other UN member states. The CND meets annually for several days in March in Vienna, in proceedings including plenary sessions, a Committee of the Whole for the discussion of proposed resolutions, and committee meetings. Each year the CND adopts resolutions following discussions which are often lengthy, since its decisions are customarily made by consensus.

The administrative body for the system is the UN Office on Drugs and Crime, which has responsibility also for the two UN crime treaties (on transnational organized crime and against corruption). UNODC has a limited "regular budget" as part of the UN system and relies for 90 % of its funding on "voluntary contributions," mainly from governments. Since these contributions are usually earmarked for specific projects, donor countries have a large say in determining the directions of the UNODC's work. In 2012, UNODC had about 500 employees, spread around the world – a smaller number than the US Drug Enforcement Agency had posted outside the USA (Room and Reuter 2012).

The International Narcotics Control Board (INCB) is a board consisting of 13 individual members elected by ECOSOC, 3 of them from a list of 5 nominated by the World Health Organization. They are supposed to serve as independent experts, not as representatives of any state; a unit within the UNODC serves as the INCB's secretariat. In addition to technical duties such as running the international market for opiate medications, the INCB has regarded itself as the "guardian of the treaties," issuing an annual detailed global report on the state of compliance as the INCB defines it (Bewley-Taylor and Trace 2006).

The World Health Organization also has responsibilities under the 1961 and 1971 treaties for providing scientific and medical expertise, particularly concerning the classification and scheduling of psychoactive substances under the conventions. According to the 1971 Convention, its assessments "shall be determinative as to medical and scientific matters." These responsibilities are primarily assigned to the Expert Committee on Drug Dependence, which is supposed to be constituted every 2 years for a process involving first prereview and then 2 years later a detailed review concerning classification of particular substances. However, due to WHO's limited resources, the Committee did not meet between 2006 and 2012. Recognizing that the present scheduling of many substances had not been reexamined in the light of scientific and other developments for many years, the most recent Expert Committee supported a proposal for each scheduled substance to be rereviewed every 20 years. In an Annex to the Committee's report, it was also pointed out that the language of the conventions does not map easily onto current scientific language concerning drugs (WHO 2012, p. 16, 23–35).

Over a number of years, the drug treaty system and the WHO drifted apart. A signal of this has been the CND's rejection in recent years of WHO recommendations on scheduling (Babor et al. 2010, pp. 213–214). Another signal of the division has been over the place of harm reduction in the treatment of drug problems. In public health in general, the reduction of harm is a central commitment

and strategy, and as the global public health agency, WHO was necessarily committed to its promotion. However, prior to 2009 the USA had insisted that the concept and term "harm reduction" not be used in the work of the international treaty agencies. After 2009, relationships between UNODC and WHO have been revitalized, including joint work on treatment guidelines (Room and Reuter 2012).

87.4 What Can Be Said About the Effects and Impact of the System?

One measure of the success of the system is its near universality, in terms of formal adherence to the treaties. Each year's INCB report notes with some pride the tally of countries which are signed up to each treaty. The desire for universality triumphed in the case of Bolivia's recent denunciation and reaccession to the 1961 treaty, despite disapproval by the INCB and other guardians of the system. Bolivia took this route to add a reservation to the treaty which would then allow Bolivians to chew coca leaves without contravening Bolivia's treaty commitments. Thwarted in an attempt to make this change by international consensus, Bolivia denounced (announced its withdrawal from) the treaty, proposing to reaccede with a reservation concerning coca chewing if the reservation was accepted (Room 2012a). If one-third of countries acceding to the treaty had objected, Bolivia's reaccession would not have gone into effect. It is a mark of the system's commitment to universality that there were only a few objections, despite considerable displeasure expressed by the INCB and others about Bolivia's reservation.

A second measure is in terms of its success in ensuring access to pain medication. For developed countries, this is not generally a problem. But the WHO has estimated that 80 % of the world's population lacks adequate access to effective pain medication (WHO 2007). Part of the problem, of course, is a lack of resources to procure or supply the medication. But another part is the indirect result of the treaty system. In consequence of the system's emphasis on law enforcement, decisions on importation of controlled drugs are often in the hands of police, who may choose to restrict or stop imports in order to impede diversion of the medicine to illicit markets. Reflecting concern about this, the most recent WHO Expert Committee decided that ketamine, a cheap and relatively safe anesthetic widely used in poor countries, should not be brought under the treaties. "Concerns were raised that if ketamine were placed under international control, this would adversely impact its availability and accessibility. This in turn would limit access to essential and emergency surgery, which would constitute a public-health crisis in countries where no affordable alternative anaesthetic is available. On this basis, the Expert Committee decided that bringing ketamine under international control is not appropriate" (WHO 2012, p. 9). Reflecting a greater priority still being placed on prohibition of nonmedical use than on the availability of needed medications, many national delegations and three regional groupings expressed concerns or regret about the WHO decision at the May 2013 meeting of the CND (IDPC 2013, p. 11).

A third measure is in terms of success in controlling legal markets. Here the system can show some success, among mixed results. The pre-Single Convention system succeeded (aided by the Depression) in substantially reducing world consumption of opium in the years prior to World War II. The current system, however, has not impeded the substantial rise in recent years in prescribed use of opioids in North America, which accounts for the lion's share of global use of prescribed opioids. In general, the conclusion of Bruun and colleagues (1975) remains true: the system's successes tend to occur where "it has been the conduct of professions and private enterprise which has been influenced." Large firms and state-licensed professionals have something to gain from cooperation with a control system, and with such levers of influence, drug control systems have had some successes, for instance, in getting chemical industries to control chemical precursors and in changing doctors' prescribing patterns when drugs, such as the barbiturates, prove to be more dangerous than was thought. The lack of any trade disputes about drugs under the system's control, in an era when free-market ideology has been dominant, might also be regarded as an unheralded success for the system.

A fourth measure, of course, is the system's degree of success in eliminating or at least reducing illicit trade, markets, and use. Here the overall result must be viewed as a failure. In 1998, the UN system set a 10-year goal of "eliminating or significantly reducing the illicit cultivation of coca bush, the cannabis plant, and the opium poppy by the year 2008." This goal remained as distant at the end of the period as it had been at the beginning (Reuter et al. 2009).

87.5 Signs and Directions of Change

The failure of the international drug prohibition system in terms of its most public goal, of eliminating or minimizing illicit markets, has been apparent for some decades. At national and subnational levels, there have been initiatives and experiments since the 1960s in moving in other directions, although these initiatives have been greatly hampered by the perceived necessity of operating within the constraints of the international system. Thus, even the Dutch "coffee shop" system for quasi-legal retail sale of cannabis, the most far-reaching attempt to move from an illicit to a regulated market, was handicapped by the "back door" problem – that cannabis which was sold under license at the front door had come in the back door illegally, since no way could be found to reconcile a legal wholesale supply with national obligations under the treaty (Korf 2008).

But there are signs of change in the early 2010s, particularly in the Americas. A diverse array of Latin American countries have shown a growing impatience with the status quo and have been willing to push against the long-standing "Washington consensus" for the status quo on drug policies. First several retired Latin American presidents, and then some sitting presidents, have expressed the need for new directions. The motivations have been diverse. In Mexico and Central America, the primary issue has been the carnage in their populations from a "war on drugs" aimed at cutting off the supply to the insatiable demand from northern neighbors.

In Bolivia, as mentioned, legalization of the folk custom of coca-leaf chewing has been a main concern. In countries like Uruguay, efforts to create a regulated legal cannabis market are aimed primarily at removing a main source of criminalization of young people. With a report from the Organization of American States (OAS) exploring alternative scenarios for the future (OAS 2013), these impulses at national levels have now taken a collective form in the region's intergovernmental agency.

At least as important have been the changes in the USA. In November 2012, votes on popular initiatives for regulated cannabis markets in Colorado and Washington (Room 2014b) began concrete processes of change likely to have lasting effects, no matter how the US federal government eventually reacts. At about the same time, trends in opinion polls among US adults for the first time showed a popular majority for legalizing cannabis (Walsh 2013). Changes in the legal status of cannabis do not, of course, deal with the drug problem as a whole. But, since three-quarters of the illicit drug users in the world use only cannabis, in numeric terms dealing with cannabis will have a large effect.

The direction and extent of any changes are still unclear. The OAS report lays out some alternative scenarios for the future. Other recent reports have laid out options for change in the treaties and have discussed more and less likely scenarios (Room 2012b), including a potential Framework Convention on Cannabis which might supersede the handling of cannabis in the Single Convention (Room et al. 2010). But, at least in the short run, it is more likely that changes will be piecemeal and country specific, rather than at the system level – whether involving changes made within the rules of the system, as in the case of Bolivia, or beyond the rules, as with cannabis buyers' clubs in Spain and other parts of Europe (Jelsma 2011) and the Colorado and Washington initiatives (Room 2014a).

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Monitoring and Evaluation of Addiction Treatment

88

Ambros Uchtenhagen

Contents

Abstract

Monitoring and evaluation (M & E) are research activities dedicated to document and analyze the processes and outcomes of addiction treatment. Before starting M & E, some conceptual issues apply, such as considering the objectives of a given treatment or treatment system, the outcome indicators to be used, the characteristics of the target population, and the basic understanding of the nature of addiction.

A range of different goals can be envisaged in M & E projects, from measuring treatment implementation and the use of the available resources to measuring efficacy and effectiveness. The overall goal in general is the improvement of services and treatment systems. The main steps in developing M & E projects are determining the research questions, the appropriate type and design of evaluation, and the resources and partners needed. Also, it is helpful to identify expected problems and obstacles.

Lists of evidence-based guidelines and instruments for evaluation are attached, as well as lists of high-quality publications reviewing the outcomes of evaluation studies.

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88.1 Introduction

Monitoring and evaluation (M & E) are essential instruments for an optimal drug demand reduction through treatment and prevention. They serve the commitment to effective interventions, which are based on scientific evidence. Only a good knowledge on the effects of interventions can provide the evidence base for an adequate substance abuse policy.

The main objective of M & E is to assess the available intervention system at country, regional, or local level, to determine its adequacy for covering the treatment needs in the respective population, and to measure its intermediate, short-term, and long-term outcomes. This is instrumental for a targeted improvement of available intervention systems, as well as for an adaptation to new challenges from changes in substance using populations and the health and social consequences of use. Monitoring trends in substance using populations out of treatment is helpful in order to observe such changes, e.g., the arrival of new drugs.

M & E also cover structural and procedural properties of services and systems, as major instrumental elements for outcomes.

M & E can also serve other purposes, such as providing arguments for legitimizing the treatment or prevention approach against repressive approaches.

88.2 Main Aspects of Monitoring and Evaluation

88.2.1 Definitions and Rationale

There are no universally accepted definitions. Monitoring and evaluation are performed in many fields of activities, such as health and education, and the aims and definitions are adjusted to the respective field. For this chapter, the following definitions and rationale apply.

88.2.1.1 Monitoring Treatment

Monitoring is an activity to continuously document defined indicators of treatment implementation and outcomes.

Rationale: to determine the level of service performance and treatment results, as a starting point for improvements and for measuring change as a result of improvements.

88.2.1.2 Process Evaluation of Treatment

Process evaluation is a one-time or repetitive activity to document how therapeutic interventions are implemented, in terms of coping with predetermined rules and criteria.

Rationale: to determine the level of service responsiveness to needs and compliance with expected performance, in order to facilitate the expected results.

88.2.1.3 Outcome Evaluation of Treatment

Outcome evaluation is a one-time or repetitive activity to document the consequences of therapeutic interventions for the target population, in terms of predetermined goals and indicators.

Rationale: to measure the intended and unintended effects of therapeutic interventions, in order to determine the value of a given intervention, a service, or treatment system to serve the expected treatment objectives.

88.2.1.4 Economic Evaluation of Treatment

Economic evaluations are a specific type of outcome evaluation. They measure the proportions of costs and benefits of an intervention, a service, or a treatment system. Costs and benefits are measured at the individual or at society level. In cost-effectiveness evaluation, effectiveness is expressed in terms of costs per unit of outcome. Cost-utility evaluation determines the gains in years and quality of life in relation to costs.

Rationale: to explore satisfaction with the results of investments made.

88.2.1.5 Meta-evaluation

The growing number of evaluation studies and their unequal quality invited an effort to review evaluation studies, on the basis of rigorous methodological analysis, resulting in reliable information about "what works" and "what works for whom."

88.2.1.6 Comparable Terms

Other terms for process and outcome evaluation, especially in the educational field, are formative and summative evaluation. Formative evaluation is typically conducted during the development or improvement of a program or course. Summative evaluation involves making judgments about the efficacy of a program or course at its conclusion.

For other and partly overlapping definitions of terms, see the referenced evaluation guidelines of World Health Organization (WHO 2000) and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA 2007).

88.2.2 Preparing for Monitoring and Evaluation (M & E)

A detailed M & E project is the key to the feasibility of data collection, to the validity of data, and to the usefulness of results. The following issues and steps must be considered before starting a project. It is recommendable to set up an M & E project in collaboration with an expert.

88.2.2.1 Conceptual Issues

Treatment Objectives

The specific objectives of a given therapeutic method or of a given program determine the type of outcome data to be collected, in order to know how far

Table 88.1 Outcome indicators

Retention rate	Measuring time in treatment
Status at discharge	Regular vs. irregular discharge (drop-out, exclusion)
Addictive behavior	Consumption patterns of legal and illegal addictive substances
Risk-taking behavior	Injecting drugs, needle sharing, unsafe sex
Health status	Changes in somatic and psychological health
Social reintegration	Changes in living arrangements, employment, social networking, criminal activities
Quality of life	Subjective wellbeing

outcome responds to the objectives. Objectives may be reduction of main substance use or any substance use, abstinence from main substance use or any substance use, health improvements, reduction or abstinence of illegal activities, social integration such as gainful employment or participating in a social network, or complete recovery.

Outcome Criteria

If not specific treatment objectives are in place, any M & E project has to determine which type of outcomes are to be measured. This may be those mentioned above, but also others such as the quality of life of patients/clients or the reduction of negative consequences of addiction at population level in terms of substance-related crime and nuisance or blood-borne infectious disease. The following is a catalogue of the most frequently used outcome indicators (adapted from EMCDDA 2007, Table 2) (Table 88.1):

The choice of outcome criteria should meet the interests of all stakeholders including the mandating and/or funding bodies for the project.

Characteristics of the Target Population

Intermediate, short-term, and long-term outcomes of therapeutic interventions are diverse for different target populations. Age, gender, level of education, level of social integration and social support, religious affiliation, health factors such as comorbidity, etc. have a potential to influence how well a person responds to a therapeutic intervention or program. Data collection therefore must be tailored to the specificities of the target groups an intervention or service is meant to serve.

Understanding Addiction

Also, the kind of data to be collected for M & E depends on how addictive behavior is interpreted. Various paradigms apply here: the use of psychotropic substances can be understood as self-medication for symptom relief (Khantzian 1997), as a special variation of self-manipulation, tailoring use to a desired state of mind, or as instrumental for self-enhancement, optimizing function and output (Harris 2007). Or else, substance use is understood as a lifestyle phenomenon, in the sense of "consumerism" or of an expression of subcultural identity. On the other side,

addiction is understood as a brain disease, following repetitive substance use resulting in structural changes (Leshner 1997) or on a vulnerability-stress model focusing on the impact of genetic and environmental factors on the brain changes (Volkow et al. 2004). For each of these paradigms, specific contextual data and patient/client characteristics are of interest in order to explain the value of intervention outcomes.

Also, understanding addiction as a chronic relapsing disorder has consequences for the design and methodology of evaluation studies (McLellan et al. 2000).

88.2.2.2 Goals of M & E Projects

M & E projects are made for a variety of purposes (see also EMCDDA 2007, Chap. 1). The purpose is relevant for the research questions to be answered by the project, the research questions are relevant for the design and methodology to be used as well as for the data which are necessary for answering the questions.

Measuring Program Implementation

A comparison is made between the intended standards of a therapeutic program or protocol and the de facto characteristics of its implementation. It includes structural and procedural aspects. Among the many issues of interest are the indication criteria, staff composition and qualifications, infrastructure and location of service, links with other services, etc. It may also include an estimation of how well the treatment needs in the regional/local population are covered.

Such projects are mainly of the process evaluation type. A recent example is part of the WHO collaborative study on substitution therapy of opioid dependence and HIV/AIDS (Lowrinson et al. 2008). Continuous monitoring of the process has the advantage to document changes made over time in terms of program implementation.

Measuring Use of Resources

In an overall purpose to make best use of available human and financial resources, M & E projects can measure the overall utilization of the treatment capacity or the utilization by the intended target population. They can compare outcomes between services receiving similar investments and serving similar populations. More difficult and demanding are economic evaluations as mentioned above.

Measuring Efficacy and Effectiveness

Efficacy of therapeutic interventions are as a rule determined by clinical trials, using a randomized controlled design. These trials provide us with data showing the relative efficacy of a given intervention or medication in comparison to another intervention or medication, if the treatment is allocated at random and the sample characteristics are comparable.

In contrast, the effectiveness of an intervention or a treatment service is defined by how well an intervention or a service works in practice and produces the desired results. It is usually measured by cohort studies including outcome evaluation with or without elements of process evaluation.

Efficacy and effectiveness studies contribute to a better knowledge on what treatment is best suitable and has the best chances for which patients/clients under which conditions and thereby to improve the indication criteria for patient/client placement.

Legitimation of Treatment

A frequent purpose of evaluation projects is demonstrating the value of a given intervention or service, in terms of desired outcomes, patient/client satisfaction, and positive economic balance of input and outcome. This can be done through a single-service follow-up study or a nonrandomized comparative study. The main issues why it is important to assure the legitimacy must be considered in the research questions and the study design.

Improvement of Services and Treatment Systems

M & E studies can provide data which allow to identify weaknesses, to initiate changes, and – in a repetitive effort – to document the intended and unintended effects of such changes. Process evaluation and qualitative data are most helpful for improvement purposes (Rush and Krywonis 1996).

88.2.2.3 Determining the Research Questions

The questions to be answered by an M & E project depend on the aims and must be made explicit, for an agreement between all stakeholders. The questions determine what kind of samples is needed, which data must be collected, and which study design is most appropriate.

Additional research questions may be included in order to address special interests by staff, funding agency, or other stakeholders. The inclusion of such questions has a potential to enhance cooperation and compliance with the main study.

The following types of research questions can be considered (see also WHO 2000, workbook 1 step 5, and EMCDDA 2007, Chap. 3):

- *Descriptive questions* for precise information about observations made
- *Normative questions* aiming at a comparison between observations and expectations (e.g., standards)
- *Impact questions* exploring the role of interventions or elements thereof for the observed outcomes

88.2.2.4 Typology of Treatment Evaluation

There is no universally accepted typology. The following is mainly based on the types presented in the EMCDDA Guidelines (EMCDDA 2007) and in the WHO/UNODC/EMCDDA Evaluation workbooks (WHO 2000).

Needs Assessment Evaluation

Needs assessment studies are used to determine and improve the coverage of treatment needs in a given population, in order to tailor treatment capacity, mix of services, and networking among services accordingly (WHO evaluation workbook 3).

Structure Evaluation

Evaluation of the appropriateness of infrastructure and other structural elements to facilitate the desired outcomes of treatment. This includes location, safety provisions, financial resources, staff composition and qualification, governance, and organization.

Process Evaluation

Process evaluation documents and analyzes how treatment is delivered. Assessment procedures, indication criteria, treatment planning, programming, qualification and attitudes of staff, continued training of staff, house rules, sanctions, etc. are some of the elements to be considered (WHO workbook 4, extensive list of available instruments for process evaluation on the EMCDDA instrument bank EIB).

Outcome Evaluation

The focus is on the consequences of treatment for patients/clients, their families, and the community. It provides information on which treatment modality has which consequences for which target groups and under which conditions. It may consider the impact on other treatment approaches. It may become relevant for treatment motivation in the target population.

Outcome is measured against predefined behavior norms (normative evaluation), baseline pretreatment status (evaluation of change during treatment), or predefined treatment goals (goal attainment evaluation). Outcome evaluation mainly uses quantitative methods (by RCTs or cohort studies), eventually a combination of quantitative and qualitative methods (WHO workbook 7, instruments on EIB of EMCDDA).

Patient/Client Satisfaction Evaluation

Patient/client satisfaction studies measure to what extent treatment provision and treatment results meet the expectations of patients/clients. They are a major source for service improvement, together with retention rates and drop-out rates (WHO workbook 6, instruments on EIB of EMCDDA).

Economic Evaluations

Various designs are used to describe and analyze economic factors in addiction treatment. Cost analysis measures the cost factors and overall costs of treatment (e.g., per patient day, per treatment episode, per treatment modality, etc.). Cost-benefit evaluation determines the relation between costs and financial benefits (e.g., in terms of reduced health and social costs in a defined posttreatment period as compared to pretreatment values). Cost-effectiveness evaluation measures costs in relation to a specific unit of outcome (e.g., significant health improvement or significant reduction in addictive behavior). Cost-utility evaluation measures the utility of treatment for patients/clients, e.g., in terms of disability adjusted life-years DALYs (Anand and Hanson 1997) or as quality adjusted life-years QALYs (Nord 1992, Whitehead and Ali 2010). For cost evaluations see also WHO workbook 5, for economic evaluations WHO workbook 8, and for instruments EIB of EMCDDA.

Formal Evaluation

This is an assessment of service compliance with professional, ethical, and legal standards.

Meta-evaluation

Meta-evaluation is made on the basis of recognized procedures to combine quantitative results from several studies about the same or similar interventions, in order to establish composite outcome scores. This allows assessing the effectiveness of a given intervention with greater confidence than on the basis of a single study.

88.2.2.5 Evaluation by Whom?

External Evaluation

Outcome or/and process evaluation of treatment services or interventions by research professionals who are independent from the evaluated agency. This is the preferred modality, because eventual bias in collecting client data is avoided and the credibility of the study is enhanced. Disadvantages in comparison to internal evaluation may be the higher costs and resistance or noncompliance of treatment staff.

Internal Evaluation (Self-Evaluation)

This can be used as an internal learning process about the treatment program or in case of restricted funds for evaluation studies. However, internal evaluation is not recommended for outcome studies, because credibility is lower in comparison to external evaluation. Collaboration with an external evaluation specialist is an advantage.

88.2.2.6 Evaluation Level and Timing

Evaluation Level

The target of M & E projects can be a specific type of intervention or therapeutic method. It can also be a specific service or setting for delivering treatment. In contrast to single intervention and service follow-up studies, a comparative evaluation focuses on the functioning and outcomes of a local, regional, or national treatment network of services or of the overall treatment system. Choosing the target implies the choice of an adequate type and design of the project.

One-Time and Repetitive Evaluation

One-time evaluation studies are frequently made for all purposes. More relevant are repeated studies or a continuous monitoring system, allowing for a documentation of specific changes in implementation and outcomes over time. However, such an approach has important cost implications. A possible compromise is the combination of a relatively simple monitoring of routine data with a more extensive evaluation study if indicated by changes in the monitoring data or after important program changes.

88.2.2.7 Resources

Estimations must be made on the amount of funds and type of manpower in order to conduct the planned M & E project, and the availability of these resources must be checked in advance, in order to avoid delays or restrictions during implementation. Also, the infrastructure for data storage and analysis must be made available.

In view of the difference in available resources between high-income and low-/middle-income countries, priority-oriented monitoring and evaluation research as well as transnational collaboration is recommendable.

Financial Resources

If an M & E study is mandated by an external agency (governmental or nongovernmental), the budget available for the study must be identified, in order to design the study accordingly. Or else, the research group planning the study has to present a budget proposal and apply to a funding agency (Research council, Foundation, Health Authority, etc.).

If there are doubts about the feasibility of the study (e.g., access to services and patients/clients), a stepwise procedure may be preferred. In this case, a separate budget for the feasibility study is needed, and the results will determine the budget of the ensuing evaluation study.

Human Resources

Which staff is needed for carrying out a planned project? Various functions must be considered: expert support for setting up the research questions and protocol, for determining the appropriate methods and instruments, for training of interviewers, etc. Staff responsible for data collection, interviewers, staff for data control and entering into a master file, statistician for data analysis, etc. are needed. It is helpful to identify staff in advance, in order to avoid delays in implementation and in order to establish a realistic budget.

Infrastructure

Access to the necessary equipment for staff and for safe storage of data is to be ensured, as well as the disposition of the appropriate software for data handling and analysis.

88.2.2.8 Partners

Most M & E project are a collaborative effort between various partners, especially in case of external evaluation of services and networks. Clear agreements on functions, responsibilities, temporal availability, and costs are recommended, eventually with written contracts.

Funding Partners

Agreements on the overall budget, bookkeeping, financial controls, timing of payments, and financial reports help to prevent misunderstandings and litigations. Such agreements should be made to protect the interests of all parties.

Therapeutic Partners

All projects on external evaluation are based on collaboration between researchers and treatment providers. Agreements are needed on the access to patient/client data and service data, access to patients/clients for external interviewers, responsible person in a given service for organizing and facilitating the research process, ownership of data, and arrangements for publishing the study results. Procedures in case of upcoming problems during project implementation should also be agreed upon in advance.

A special situation is created in case of a systematic evaluation at the system level involving all or selected treatment providers.

Research Partners

In case multiple researchers or research groups are involved, a clear working arrangement should identify the functions, tasks, and responsibilities of the individual persons. If a service provider hires a researcher or research group for an internal or external evaluation or monitoring system, there is also a need to identify the various functions, tasks, and responsibilities.

88.2.2.9 Expected Obstacles

Most problems occurring during project implementation are due to missing or incomplete preparation. However, even a carefully prepared project may meet some obstacles. Some of the frequent ones are mentioned here.

Compliance with Protocol

Staff involved in project implementation may disregard details of the research protocol and thereby weaken data reliability, even if well instructed. This may also happen in case of changes of staff. Tutoring staff activities over the entire duration of the project helps to avoid such failures. Also, efforts to make a strong evaluation culture at the system level acceptable will contribute essentially to overcome this type of obstacle.

Resistance from Patients/Clients

One of the most common problems is the refusal to participate in a randomized study, resulting in an unacceptable degree of sample selectivity. This is especially to be expected if a control group with placebos or other forms of low therapeutic value are used or patients/clients are not confident that their data will be well protected against external parties, for example, in studies involving illicit substance use and/or drug-related criminal activities. Informed consent should cover not only aims and design of the study but also measures taken to guarantee data protection.

External Interference

It may happen that family members of patients/client or other third parties raise opposition against an M & E project, on the basis of ethical concerns. It is advisable to have an explicit permission from an ethical committee, if not already prescribed by law.

88.2.3 Implementation of M & E

88.2.3.1 Available Guidelines and Instruments for Treatment Evaluation

International Guidelines for Treatment Evaluation

From the number of evaluation guidelines, a few are mentioned here, on the basis of their wide international applicability. It is highly recommendable to consult one or more guidelines before starting an M & E project.

WHO/UNODC/EMCDDA Evaluation of Psychoactive Substance Use Disorder Treatment Workbook Series (WHO 2000)

This publication consists of a series of workbooks intended to educate program planners, managers, staff, and other decision-makers about the evaluation of services and systems for the treatment of psychoactive substance use disorders. The objective of this series is to enhance their capacity for carrying out evaluation activities. The broader goal of the workbooks is to enhance treatment efficacy and cost-effectiveness using the information that comes from these evaluation activities.

EMCDDA Guidelines for the Evaluation of Treatment in the Field of Problem Drug Use. A Manual for Researchers and Professionals (EMCDDA 2007)

This publication provides basic information on the options, elements, and procedures of drug-related treatment evaluation. It also contains an overview of European and international evaluation and research networks.

Instruments for Treatment Evaluation

The EMCDDA evaluation instrument bank EIB covers a range of available instruments ready for data collection, including information on the target group specificity, the available languages (mostly English), copyrights, and eventual restrictions for use. Instruments are available for needs assessment and planning, for mediating and risk factors, for process and outcome evaluation, for patient/client satisfaction, and for staff knowledge and satisfaction.

The WHO/UNODC/EMCDDA evaluation workbooks present many instruments in the context of the various steps and approaches of treatment evaluation (WHO 2000).

A recent instrument for assessing and improving addiction treatment at the system level is the WHO Substance Abuse Instrument for Mapping Services SAIMS (ongoing).

88.2.3.2 Adaptation of Guidelines to Special Situations

Recommendations made in guidelines are not always responding to the specificity of a given project. However, major deviations from recommendations should be highlighted and reasons should be given. Special situation may arise from restricted resources or ethical restrictions. While there is some research on how to adapt treatment guidelines to clinical practice (Graham and Harrison 2005), no such systematic effort is known for evaluation guidelines.

88.2.3.3 Meta-analysis and Reviews of Evaluation Studies

Two organizations have been established in order to review and analyze evaluation studies selected for their rigorous methodology: the Cochrane Collaboration and the Campbell Collaboration.

The Cochrane Collaboration (www.cochrane.org) has its focus on evaluation of medical treatments, while the Campbell collaboration (www.campbellcollaboration.org) has its focus on social interventions.

Both organizations make their reviews available in their respective online libraries (www.thecochranelibrary.com, www.campbellcollaboration.org/library/php). A growing number of reviews cover pharmacological and psychosocial treatments in addiction and their outcomes.

88.2.3.4 Study Designs and Protocols

The choice of the appropriate study design depends on the research questions and on the available resources. The most frequently used designs are presented below (Table 88.2) (see also EMCDDA 2007, Chap. 3, Table 1).

Cross-Sectional Studies

One-time studies to compare treatment services, treatment populations, and treatment outcomes at a given moment in time (e.g., intermediate outcomes during treatment or after terminating treatment). Cross-sectional studies cannot describe processes of change over time.

Cohort Studies

Cohort studies describe the course and outcomes of treatment populations which receive their treatment as usual in practice, not allocated by randomization (observational or "naturalistic" studies). Cohort studies use retrospective or prospective data.

Longitudinal Retrospective Studies

Anamnestic data on pretreatment characteristics and outcomes of treatment populations are used to describe the therapeutic results of a given intervention/service alone or in comparison with other interventions/services. This type of study is more economic in comparison to prospective studies, which need multiple, at

Table 88.2 Main types of study designs

Cross-sectional studies	Comparing interventions/services at a given point in time
Cohort studies	Comparing measurements of single interventions/services or several interventions/services at multiple points in time (baseline data, intermediate outcomes, outcomes at follow-up)
Randomized controlled studies RCT	Comparing outcomes if interventions are assigned to patients/clients at random, not as in clinical practice (observational studies)
Quasi-experimental studies	RCT with special randomization procedures

least two measurement points in time; its usefulness however depends on the availability and quality of anamnestic data.

Longitudinal Prospective Studies

Collecting pretreatment, during-treatment, and posttreatment data at different time-points allows a focused and detailed description of the treatment process and results. It avoids biased or missing baseline data and therefore provides for more reliable results of effectiveness. Prominent national studies comparing cohorts from different treatment settings are the DATOS study in USA (Simpson 2003) and the NTORS study in the UK (Gossop et al. 2003).

Randomized Controlled Studies

Randomized controlled studies (RCT) are the "gold standard" for evaluating specific therapeutic modalities and medications in clinical research. Patients are allocated "at random" to an experimental group or to a control group, thereby minimizing selection factors between the two groups. As not all patients are willing to accept randomization, especially if not allocated to their preferred intervention, this design may suffer from refusal to participate or from elevated drop-out rates. Randomized studies allow to identify the effectiveness of a modality or medication, but do not provide results of effectiveness due to their selectivity. An updated collection of RCTs on addiction treatment can be found in the Cochrane library.

Double-Blind Randomized

If assignment to the experimental or the control group is not revealed to patients and therapists, their preferences are better (although not completely) ruled out and the study gets more reliable results about comparative treatment efficacy. This design is mainly used for a comparison of medications; psychosocial interventions cannot be "blinded."

Quasi-experimental Designs

Instead of comparing two or more modalities, the effects of an experimental modality can be compared to the course while waiting to be accepted for that modality. In this case, the control group receives treatment as usual or no treatment while waiting.

In the Zelen design, informed consent is only asked after randomization and only from patients assigned to the experimental group, while those who are randomized to treatment as usual need not to consent to participation in the study (Torgerson and Roland 1998). This design makes it easier for patients to participate, because they do not have to consent to be randomized. Of course, blinding is not possible in this design.

Another design uses different sequences of treatment modalities, e.g., A-B-A compared with B-A-B or B-B-A.

Role of Methodology for the Quality of Results

Grading of Evidence

Treatment evaluation searches for scientific evidence which can be used as a basis for therapeutic recommendations. However, there are grades of evidence,

Table 88.3 Grading of evidence

Grade	Definition
A	Highest degree of evidence: review from multiple randomized controlled studies (RCT) with convergent results
B	High degree of evidence; results from single RCT and controlled clinical studies
C	Moderate degree of evidence: prospective comparative longitudinal studies (observational studies without control design)
D	Low degree of evidence: single intervention/service follow-up studies, case studies
E	Very low degree of evidence: nonsystematic observations
Z	Not known

depending on the type of study design (see also GRADE working group 2004). The following is an adapted version (Table 88.3).

Standards for Consensus Building

Where evidence from quantitative studies is not available or feasible, recommendations for good practice are mainly based on expert opinion. In order to optimize the consensus building process, rigorous rules have been established (AGREE II 2009).

88.2.3.5 Quantitative and Qualitative Methods

Quantitative Methods

Quantitative methods are used for outcome evaluation. They consist in collecting empirical data via standardized instruments (surveys, questionnaires, pre-post tests) for statistical analysis and mathematical modelling and in producing numerical results (statistics, percentages) which answer specific research questions. Data may come from existing databases (secondary data) or are collected directly from treatment samples (face to face, per telephone, or electronic media). Questionnaires may be self-administered or administered by trained interviewers. Sample size and homogeneity, reliability and validity of data, and appropriate statistical methods and models are essential for representative results.

Not all patients/clients who participate in a randomized evaluation study are compliant with the study protocol and available for follow-up data collection. Two concepts are therefore used for statistical analysis: the intention-to-treat concept (ITT) includes all participants who have been randomized, ignoring noncompliance and withdrawal, while the per-protocol concept includes only participants without any major protocol violations (Gupta 2011).

Qualitative Methods

Qualitative methods are mainly used for process evaluation. When indicating problem areas in the provision of treatments, they can also be useful for improvements and for generating new research questions. They provide information for the construction of questionnaires in process and outcome evaluation, and they can be used for the interpretation of quantitative findings (Neale et al. 2005).

The main methods are participant observation, semi-structured interviews, focus groups, and narrative research (see EMCDDA 2007). A standardized method for the selection of interview and focus group partners is the theoretical sampling model, allowing for the broadest possible spectrum of views and perspectives (Glaser and Straus 1967).

88.2.3.6 Use of Results

It is advisable to determine at an early stage of an M & E project how the results will be communicated, by whom and how. This includes issues like data ownership and authorship in publications. In order to avoid later litigations, all agreements should be documented in written.

A first start to communicate evaluation results are intermediate and comprehensive final reports; for recommended components see WHO 2000 (workbook 2, step 4) and the EMCDDA Guidelines for treatment evaluation (EMCDDA 2007, Chap. 6). Reports must at least be accessible to all stakeholders of an evaluation project. On the basis of the final results, a publication plan can help to make the best use of those. The scientific community is best reached by publications in peer-reviewed journals, and a wider audience eventually by books, good practice documents (e.g., UNODC 2008), pamphlets, mass media articles, etc.

Once the results are known, it should also be discussed what they mean and to whom they might be communicated in order to optimize their potential impact on treatments, on service planning and improvement, on treatment policy, etc.

88.2.3.7 Checklists for Assuring the Evaluation Process

All those involved in planning and implementation of a given project can profit from checklists which help to keep all elements of the project under control. The EMCDDA Guidelines for treatment evaluation present useful checklists for the preparation and implementation, as well as for the evaluation process (EMCDDA 2007, Chap. 5).

88.2.4 Treatment Outcomes: Selected Evidence-Based Guidelines and Systematic Reviews

- Effectiveness of Therapeutic Communities: a systematic review (Malivert et al. 2012)
- Principles of Drug Dependence Treatment. A Research Based Guide (NIDA (2012)
- Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence. (WHO 2009)
- Contemporary Drug Abuse Treatment. A Review of the Evidence Base (UNODC (2002).

88.2.4.1 Cochrane Library (Selected Reviews)

- Psychological therapies for pathological and problem gambling (2011)
- Methadone for non-cancer pain in adults (2012)

- Psychosocial interventions to reduce alcohol consumption in concurrent problem alcohol and illicit drug users (2012)
- Nicotine replacement therapy for smoking cessation (2012)
- Mobile phone-based interventions for smoking cessation (2012)
- Combined pharmacotherapy and behavioral interventions for smoking cessation (2012)
- Psychosocial interventions to reduce alcohol consumption in concurrent problem alcohol and illicit drug users (2012)
- Psychosocial interventions for benzodiazepine harmful use, abuse and dependence (2012)
- Effects of psychostimulant drugs on cocaine dependence (2010)
- Acamprosate for alcohol dependence (2010)
- Opioid antagonists for alcohol dependence (2010)
- Psychosocial interventions for reducing injection and sexual risk behavior for preventing HIV in drug users (2010)
- Psychosocial interventions for people with both mental illness and substance abuse (2010)
- Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence (2008)
- Psychosocial interventions for cocaine and psychostimulant amphetamines related disorders (2007)
- Alcoholics Anonymous and other 12-step programs for alcohol dependence (2006)
- Methadone maintenance at different dosages for opioid dependence (2003)

88.2.4.2 Campbell Library (Selected Reviews)

- Effects of early, brief, computerized interventions on Risky Alcohol and Cannabis Use Among Young People: A Systematic Review (2013)
- The Effectiveness of Incarceration-Based Drug Treatment on Criminal Behavior: A Systematic Review (2012)
- Brief Strategic Family Therapy for Young People in Treatment for Non-Opioid Drug Use (2012)
- Effects of drug substitution programs on offending among drug addicts (2009)
- Case management for persons with substance use disorders (2009)
- Motivational interviewing for substance abuse (2009)

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Cochrane collaboration www.cochrane.org, Cochrane library www.thecochranelibrary.com

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Section VII

Behavioural Addictions and Management Applications

Nady el-Guebaly and Hermano Tavares

Behavioural Addictions and Management Applications: An Introduction

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Nady el-Guebaly and Hermano Tavares

This section is dedicated to the increasing recognition of the behavioral addictions as a significant component of our field of practice and windows into human nature without the effect of substances. The inclusion of gambling disorder under the new DSM-5 diagnostic code of substance-related and addictive disorders as well as the recognition of Internet gaming disorder as a "condition for further study" are but examples of the awareness of an expanding empirical basis. At the same time, the increasing range of behaviors susceptible to develop from an excessive engagement to a habitual or compulsive pattern behooves us to seek for common as well as distinct features.

Two overview chapters investigate the empirical "state of the science." Drs. Yau, Leeman, and Potenza review the "biological underpinnings of behavioral addictions" including frontostriatal brain imaging findings, the implication of neurotransmitters and genetic heritability, as well as their potential in management.

Drs. Mudry, Stea, and Hodgins conduct a similar analysis of the role of "psychological underpinnings" in the development and perpetuation of the disorders. The comparative evidence of factors such as impairment of control, craving, expectancies, motives, and personality traits is described.

The next seven chapters address common and distinct features of currently recognized clinically significant behaviors.

Dr. Echeburúa's chapter ▶ Chap. 92, "Clinical Management of Gambling Disorder" details the current psychological treatment options including behavioral and

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cognitive behavioral therapies, motivational enhancement therapies, and relapse prevention. The role of Gamblers Anonymous is also described. The trials of various pharmacotherapies are reviewed and their challenges described.

It is commonly recognized that only a small proportion of individuals suffering from disordered gambling seek formal treatment. The section includes an encouraging vignette by Drs. Bowden-Jones and Smith describing their National Problem Gambling Clinic in London along with a proposed list of activities to ensure high-quality service delivery.

The next two chapters detail the intertwined investigations of electronic media. Drs. Achab et al. review the screening tools, determinants, and treatment approaches related to Internet addiction. An interesting discussion of the Internet as a vehicle for possible addictive products is included and is of relevance to the expanding social impact of this medium. Drs. Billieux et al. focus next on the dysfunctional involvement in video games and more specifically the prevailing massively multiplayer online role-playing games (MMORPGs). Structural characteristics and their addictive potential are described as well as psychological and neurobiological determinants. Reviews of clinical trials from China and the Western world are identified.

The last three chapters are an intriguing exploration of three "required" behavioral needs, i.e., shopping, sex, and food, and the determinants of their evaluation into disorders. Drs. Filomensky and Tavares review the epidemiological challenge, assessment scales, comorbidities, clinical manifestation, and determinants of compulsive buying disorders. The existing pilot treatment trials are identified.

Drs. Amadala and Hertzsprung provide a sensitive review of the evolution of excessive and maladaptive sexual behaviors into the diagnostic syndrome of sex addiction. Available screening and assessment instruments are described as well as a synopsis of etiological determinants and comorbidities. The prevailing psychosocial approaches and a laudable search to validate staff training are outlined as well as the current pharmacological trials.

The section's concluding chapter is an insightful discussion of the association between binge eating, obesity, and addiction. This interaction has come to prominence as a result of the public concern over the epidemic of obesity rising in North America and the identification of addictive features in the development of binge eating. Intriguing common neurobiological and psychosocial features are identified as well as a brand new field of investigation into the phenomenon of food addiction and its optimal management.

This section hopefully conveys the potential for insights of behavioral addictions as windows on human nature without the effect of substances. Each new behavior brings its new insights, but we should beware of the public concern over pathologizing an ever expanding list of behaviors. The section merely makes reference to exercise and work as other candidate behaviors; there are others.

A comprehensive biopsychosociocultural conceptualization of these disorders is critical, and the relative significance of each of these components is yet to be determined. In sum, current or potential candidates for a behavioral addiction have to present solid evidence of the involvement of the brain reward circuitry as

the basis for a shared psychopathology involving a decision-making bias and inhibitory control deficits.

Besides the recognition of gambling disorder as an addiction, the new DSM edition also acknowledges the prominence of craving in the addiction process. As we approach a better model of addiction, we shall be able to depend less and less on a model based upon negative consequences and avoid the perils of a circular logic, i.e., it is an addiction because it is harmful and it is harmful because it is an addiction. Along with craving, the careful reader will notice that the two other implicit concepts crosscutting the chapters from this section are loss of control and compulsion (defined as repetitively performing a behavior as a strategy to deal with an emotional imbalance). Starting with this triad, we may get closer to an evidence-based phenomenological model of addiction, while distancing from a harm-based model, which may be unduly vulnerable to ever changing cultural values and judgment calls (take, e.g., the recent evolution of the gambling perspective from frowned upon behavior to government embraced leisure activity).

That is not to deny the obvious impact of sociocultural factors especially in the determination of new behavioral addictions such as Internet and video gaming. Even in the case of essential behaviors such as sex, eating, and shopping, never before in history have individuals and communities had a wider access to services, products, and credit. Our "information" society suffuses people with news about novel and potentially gratifying behaviors, shortening the time to adequately ponder and decide.

Finally, besides perfecting and broadening the contours of the addiction model, behavioral addictions may challenge previous widely accepted treatment goals such as abstinence. Popular goal posts promoted by 12-step-based programs such as "avoid the first drink" or "avoid the first dose" become unrealistic when expanded to "avoid the first log-on," "avoid the first purchase," and "avoid intercourse," and in the case of compulsive eaters, "avoid the first bite" is an utterly impossible goal! Compulsive eaters anonymous meetings discuss "avoiding the first compulsive bite," which relates to eating when under the influence of an emotional turmoil in an unconscious attempt to deal with it, which will likely lead to loss of control. Clusters of components/symptoms must be identified for each of these behaviors in order to build tailored preventive and treatment strategies more effectively than current broader behavior-focused approaches.

Biological Underpinning of Behavioural Addictions and Management Implications

90

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Contents

Abstract

Neurobiological and clinical data indicate that maladaptive engagement in certain behaviors warrants consideration as "behavioral" or non-substance addictions. The present chapter reviews existing neurobiological and genetic/family history evidence for behavioral addictions involving gambling, Internet use, video-game

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play, sex, eating, and shopping. At a neurochemical level, behavioral addictions may involve dysregulation of serotoninergic, dopaminergic, noradrenergic, and opioidergic systems. At a neurocircuitry level, findings suggest dysfunction in brain regions associated with the mesolimbic dopaminergic pathway and frontal areas; disruption in these circuits could lead to disadvantageous decision-making, impaired inhibition, and increased cue-induced craving. While a genetic understanding is at an early stage, genetics/family history data support heritability for behavioral addictions and suggest genetic overlaps with other psychopathologies. As this represents an emerging area of research, data remain sparse in multiple domains. An improved understanding of behavioral addictions will help in establishing appropriate nomenclature and enhance the ability to recognize, prevent, and treat these disorders more effectively.

90.1 Introduction

While the term addiction has traditionally been associated with excessive alcohol and drug use (Maddux and Desmond 2000), the Latin word (*addicere*) from which it is derived was not linked to substance use. Addiction professionals and the public are recognizing that certain behaviors bear resemblance to alcohol and drug dependence, and data have been forwarded that these behaviors warrant consideration as non-substance or "behavioral" addictions (Frascella et al. 2010; Karim and Chaudhri 2012; Potenza 2006). Excessive engagement in behaviors such as gambling, Internet use, video-game play, sex, eating, and shopping may represent addictions (Holden 2010), with a minority of individuals displaying such habitual or compulsive engagement (Brewer and Potenza 2008; Chambers et al. 2007). Some of these behaviors were considered as "Impulse Control Disorders Not Elsewhere Classified" in the *DSM-IV-TR*, a separate category from substance use disorders (SUDs) (American Psychiatric Association 2000). Shaffer et al. (2004) proposed that addiction should be considered as a syndrome with multiple opportunistic expressions (e.g., substance abuse, pathological gambling, and food addictions). Aided by data from neurobiological studies, this view has gained momentum in the past decade and has led to the consideration of categorizing substance and non-substance-related addictions under one diagnostic category, "Substance Use and Addictive Disorders," in the recently published *DSM-5* (American Psychiatric Association 2013). Establishing nomenclature and criteria for behavioral addictions may enhance our capacity to recognize and define their presence.

Biochemical, functional neuroimaging, genetic, and pharmacological research in substance addiction has implicated several neurobiological processes. Multiple neurotransmitters (e.g., serotonergic, dopaminergic, noradrenergic, and opioidergic) are thought to play a role in the pathophysiology of substance addictions (Koob and Volkow 2010; Potenza 2008). For example, dysregulated dopamine systems, which are involved with learning, motivation, and salience of stimuli and rewards, and serotonin (5-HT) systems, implicated in behavioral control, may significantly contribute to addictive disorders (Fineberg et al. 2009; Potenza 2008). Prolonged engagement

in an addictive behavior may lead to a reduction of sensitivity to biological rewards and decrease an individual's perceived control over seeking and eventual engagement in the behavior. At the neurocircuitry level, the mesolimbic dopaminergic pathway (linking the ventral tegmental area (VTA) to the nucleus accumbens (NAc)) and frontal areas are thought to be critical components of the decision-making circuitry in risk-reward assessment (Goldstein and Volkow 2011; Hyman et al. 2006). Preclinical and clinical works suggest that disruptions in these regions could lead to disadvantageous decision-making (e.g., choosing immediate gains versus long-term consequences), impaired ability or willingness to inhibit response to drugs/addictive behaviors when exposed to them, and increased drug- and cue-induced craving (Everitt and Robbins 2005; Goldstein and Volkow 2002; Koob and Volkow 2010; Volkow and Fowler 2000).

Research also indicates genetic effects on the use and misuse of substances (Kreek et al. 2005; Tsuang et al. 1996). Several putative risk genes have been identified. For example, the A1 allele of the Taq1A polymorphism of the dopamine D2-receptor (*DRD2*) gene, which is associated with measures of impulsivity and behavioral inhibition, and the low-transcribing short allele of the serotonin transport gene (*5HTTLPR*), which is associated with moderating the impact of stressful life events on risk of psychiatric conditions such as depression and anxiety (Kendler et al. 2012), have shown associations with addictions in some but not all studies. However, as allelic variants of the *DRD2* are in linkage disequilibrium with another gene (*ANKK1*), the precise biological factors underlying the associations warrant additional study (Leeman and Potenza 2013).

Behavioral addictions frequently co-occur and appear to share important elements with substance-related addictions (Grant and Potenza 2012). In terms of phenomenology, both behavioral and substance addictions may be thematically categorized along four domains: craving, compulsion, diminished control, and persistence of behaviors despite negative consequences (Potenza 2006; Shaffer et al. 2004). Moreover, both have been characterized as disorders of motivation, reward, and decision-making (Chambers et al. 2007; Redish et al. 2008). Growing evidence, particularly in pathological gambling, indicates that behavioral addictions share overlapping neurobiological mechanisms and genetic contributions with substance addictions (Kühn et al. 2011; Potenza 2008; Volkow et al. 2012). However, differences have also been observed, and the extent to which findings from substance addictions extend to individual behavioral addictions may differ.

The present chapter will review existing neurobiological and genetic/family history evidence pertaining to behavioral addictions in attempt to shed light on these emerging mental health problems from a neuroscientific perspective. Specifically, the family history findings relating to pathological gambling, Internet addiction disorder, problematic video-game playing, hypersexual disorder, food addiction, and compulsive shopping. As this is an emerging area of research, data are sparse in some domains. Similarities and differences with substance-addiction findings are highlighted. Epidemiologies are addressed briefly, and more detailed descriptions of clinical features and treatment methods can be found in the following chapters. An overview of the neural systems, neurochemistry, and genetic results can be found in Tables 90.1, 90.2, and 90.3, respectively.

Table 90.1 Overview of neural system results for selected behavioral addictions, with a focus on fronto-striatal findings

Behavioral addiction	Key results	Similarities and differences with key results in substance use disorders
Pathological gambling	*Frontal areas*	Between-group differences observed in SUD and control comparison subjects with many tasks indicating reduced frontal activity, but precise nature of differences warrants additional study
	Cognitive tasks: most findings suggest reduced activity in multiple frontal regions in PG, but also some suggesting increased activity and negative findings	
	Cue-induction studies: suggest differences in activity, but the precise nature of differences warrants additional study	
	Striatal areas	
	Cognitive tasks: reduced ventral activity to reward anticipation	Many findings suggest reduced ventral striatal activity in individuals with SUDs compared to controls
	Cue-induction studies: mixed with some studies showing reduced striatal activity in PG compared to controls	
	Others: ventral striatal activity inversely correlated with impulsivity measures and problem-gambling severity	
	White and gray matter: poorer white matter integrity in multiple regions; no volumetric differences in gray or white matter between PG and controls	Poorer white matter integrity and decreased gray matter volumes in SUDs
Internet addiction disorder	*Frontal areas*	
	Cognitive tasks: EEG studies indicate diminished efficiency of response inhibition	Underactive feedback valence in individuals with SUDs
	Resting state: differences in regional homogeneity in multiple frontal regions, but the precise nature of differences warrants additional study	Preliminary studies suggest reduced regional homogeneity in SUDs
	White and gray matter: lower gray matter density in multiple regions including dlPFC, ACC, and insula; differences in white matter integrity between IAD and controls, but the precise relationship is unclear	Poorer white matter integrity and decreased gray matter volumes in SUDS
Problematic video-game playing	*Frontal areas*	Underactive feedback valence in individuals with SUDs
	Cognitive tasks: EEG studies indicate diminished efficiency of response inhibition	

(*continued*)

Table 90.1 (continued)

Behavioral addiction	Key results	Similarities and differences with key results in substance use disorders
	Cue-induction studies: greater activation of multiple frontal areas including the OFC and dlPFC	Between-group differences observed in SUD and control comparison subjects, but precise nature of differences warrants additional study
	Striatal areas	
	Cognitive tasks: greater activation of ventral striatum among frequent (versus infrequent) gamers	Reduced ventral striatal activity typically reported; however, findings may differ per task
	Cue-induction studies: increased activity in the ventral striatum compared to controls	
	Gray matter: greater striatal gray matter volume among frequent (versus infrequent) gamers	Decreased striatal gray matter volume in SUDs
Hypersexual disorder	*White matter*: higher integrity of lower superior frontal region	Poorer white matter integrity in SUDs
Food addiction	*Frontal areas*: increased OFC activation in response to food cues but decreased activity upon ingestion of food among individuals with high food addiction scores	Between-group differences observed in SUD and control comparison subjects, but precise nature of differences warrants additional study
	Other regions: increased ACC and amygdala activation in response to food cues among individuals with high food addiction scores	Evidence for ACC activity in risky decision-making in SUDs; amygdala activity associated with trait craving in SUDs
Compulsive shopping disorder	*Striatal areas*: increased activity in ventral striatum upon product presentation	Reduced ventral striatal activity typically reported; however, findings may differ by task
	Other regions: reduced activity in insula and ACC during price presentation	Insula activity in response to substance cues; evidence for ACC activity in risky decision-making in SUDs

PG pathological gambling, *SUDs* substance use disorders, *IAD* Internet addiction disorder, *PVG* problematic video-game playing, *EEG* electroencephalography, *dlPFC* dorsolateral prefrontal cortex, *ACC* anterior cingulate cortex, *OFC* orbitofrontal cortex

90.2 Behavioral Addictions

90.2.1 Pathological Gambling

In the last decade, pathological gambling (PG) has developed a strong research base in the wake of worldwide legalized gambling and concerns over gambling's possible health and social impacts. Similar to substance addictions, PG can include preoccupations with gambling, gambling with greater amounts of money to receive the same level of desired experience (tolerance), repeated unsuccessful efforts to control or stop gambling, restlessness/irritability when trying to stop gambling

Table 90.2 Overview of neurochemistry results for selected behavioral addictions

Behavioral addiction	Key results	Similarities and differences with key results in substance use disorders
Pathological gambling	*Dopamine*: dopamine implicated but the precise nature unclear; negative between-group findings for differences in D2-like receptor availability at rest; differential response to dopamine antagonist administration in PG, although findings mixed; individuals differences in dopamine release and function may contribute to impulsivity and decision-making	Dopamine release has been related to substance use; reduced D2-like receptor availability in SUDs typically reported; mixed clinical findings with dopamine antagonists; individuals differences in dopamine release and function thought to contribute to variability in impulsivity and risky decision-making in SUDs
	Serotonin: mixed results with SSRIs; possible individual differences in serotonin function	Evidence suggest between-group differences in serotonergic function; mixed clinical results with SSRIs, suggest possible individual differences
	Opioids: positive clinical findings with opioid antagonist suggests involvement of opioid system	Multiple positive clinical findings suggest role for opioid systems, particularly for opiate and alcohol dependence
	Other neurotransmitters: noradrenergic levels elevated among PG; preliminary positive clinical findings with glutamate antagonist suggest involvement of glutamatergic systems	Findings suggest elevated noradrenergic levels in some SUDs; positive clinical findings suggest role for glutamatergic systems
Internet addiction disorder	*Dopamine*: decreased striatal dopamine transporter expression in IAD; limited findings suggest differential D2-like receptor availability in the striatum – however, results differ between subdivisions	Mixed findings regarding levels of dopamine expression in striatum; reduced D2-like receptor availability in SUDs typically reported
Problematic video-game playing	*Dopamine*: limited and preliminary findings suggest increased dopamine release in ventral striatum during video-game play; the role of dopaminergic activity in PVG has not been directly investigated	Dopamine release has been related to substance use, and most studies indicate between-group differences in dopaminergic activity
Hypersexual disorder	*Serotonin*: positive results from clinical trials with SSRIs	Mixed clinical results with SSRIs with some positive and others negative
	Opioids: initial positive findings for high doses of opioid receptor antagonist; however, positive results not long-lasting	Multiple positive clinical findings suggest role for opioid systems in SUDs
Food addiction	*Dopamine*: dopamine release related to food and food cues; reduced D2-like receptor availability in obese individuals and mice; animal models of food addiction suggest consumption of hyperpalatable	Dopamine release has been related to SUDs, and most studies indicate between-group differences in dopaminergic activity; decreased dopamine release and receptor

(*continued*)

Table 90.2 (continued)

Behavioral addiction	Key results	Similarities and differences with key results in substance use disorders
	foods decreased dopamine release and receptor expression following withdrawal; the role of dopaminergic activity in food addiction has not been directly investigated in humans	expression following substance use withdrawal, particularly in striatal regions
	Serotonin: positive findings in open-label and double-blind studies with SSRIs for BED	Mixed clinical results with SSRIs with some positive and others negative
	Opioids: positive findings for high doses of opiate antagonist in rodents but the precise nature unclear; different nutrients may have different effects on the opioid system	Multiple positive clinical findings suggest role for opioid systems in SUDs
Compulsive shopping disorder	*Serotonin*: some positive results from clinical trials with SSRIs, while controlled results for others have been typically negative	Mixed clinical results with SSRIs with some positive and others negative

PG pathological gambling, *SUDs* substance use disorders, *IAD* Internet addiction disorder, *PVG* problematic video-game playing, *SSRIs* selective serotonin reuptake inhibitors, *BED* binge eating disorder

(withdrawal), and interferences in major areas of life functioning. PG criteria also include gambling to escape from a dysphoric state, gambling to regain gambling-related losses ("chasing" losses), lying in significant relationships about gambling, and relying on others to fund gambling (American Psychiatric Association 2000). Engaging in illegal activities in order to fund gambling was a criterion in the DSM-IV-TR but was eliminated in DSM-5, thus reducing the threshold of inclusionary criteria from 5 of 10 to 4 of 9, and the disorder has been moved to an "Addiction and Related Disorders" category. High comorbidity rates for PG and substance addictions have been observed, with a recent meta-analysis suggesting a mean co-occurrence of 57.5 % (Lorains et al. 2011).

90.2.1.1 Neural Systems

The basis of PG is likely multifactorial. Changes in processing of gambling cues and gambling decisions, including those relating risk/reward decision-making, reward processing, and impulse control, are likely contributing factors (van Holst et al. 2010). Neuroimaging studies have typically investigated frontal and striatal circuits, although several lines of evidence also suggest the involvement of other regions.

Neuropsychological findings in PG have indicated impaired decision-making and deficits in executive functions compared to controls (van Holst et al. 2010). Functional magnetic resonance imaging (fMRI) studies during cognitive tasks have implicated frontal areas; in particular, multiple investigations have observed

Table 90.3 Overview of selected genetic results for selected behavioral addictions

Behavioral addiction	Key results	Similarities and differences with key results in substance use disorders (SUDs)
Pathological gambling	*Family history*: PG highly heritable; twin studies indicate genetic factors may share similar magnitudes with or contribute more than environmental factors to overall risk for developing PG	SUDs highly heritable; twin studies indicate genetic and environmental factors share similar magnitudes of influence on overall risk for developing a drug use disorder
	Molecular genetics: preliminary findings suggest genetic polymorphisms related to dopamine (DRD2) and serotonin transmission (5HTTLPR, MAO-A); recent genome-wide association study did not identify different contributions to individuals with PG	Associations with polymorphisms related to dopamine and serotonin transmission; genome-wide associations indicate some different contributions to individual SUDs
Internet addiction disorder	*Molecular genetics*: preliminary findings suggest overexpression of SS-5HTTLPR in males with IAD	Associations with serotonin transporter gene polymorphisms
Problematic video-game playing	*Molecular genetics*: preliminary findings suggest presence of Taq1A polymorphism of DRD2 receptor gene and low activity COMT alleles more likely in males with online PVG	Links between SUDs and Taq1A polymorphisms, but not universally replicated; the low activity COMT variant linked to various SUD (e.g., nicotine, methamphetamine, and alcohol)
Hypersexual disorder	*Family history*: more likely to have parent with hypersexual disorder; more likely to have first-degree relative with SUDs	Individuals with SUDs more likely to have first-degree relative with various SUDs and psychopathology
Food addiction	*Family history*: obesity tenfold more likely in people with an obese first-degree relative	Individuals with SUDs more likely to have first-degree relative with various SUDs and psychopathology
	Molecular: obese individuals with BED, compared to non-BED, had lower frequencies of the Taq1A1 polymorphism of DRD2 receptor gene and higher frequencies of the G118 polymorphism of the mu-opioid receptor gene (OPRM1); overexpression of SS-5HTTLPR in overweight adolescent	Associations with polymorphisms related to dopamine and serotonin transmission; OPRM1 polymorphisms may mediate reward effects of drugs of abuse (e.g., opiates, alcohol, and heroin); however, result in clinical populations have been mixed
Compulsive shopping disorder	*Family history*: relationship to parental history of CSD and first-degree relative with SUDs	Individuals with SUDs more likely to have first-degree relative with various SUDs and psychopathology
	Molecular: negative findings for 5HTTLPR polymorphisms	Associations with serotonin transporter gene polymorphisms

PG pathological gambling, *SUDs* substance use disorders, *IAD* Internet addiction disorder, *PVG* problematic video-game playing, *CSD* compulsive shopping disorder, *DRD2* dopamine receptor D2, *5HTTLPR* serotonin transporter-linked polymorphic region, *MAO-A* monoamine oxidase A, *COMT* catechol-O-methyltransferase, *OPRM1* opioid receptor, mu 1

differences in ventromedial prefrontal cortex (vmPFC) function in PG. For example, PG (versus control) subjects have exhibited relatively diminished vmPFC activation during presentation of incongruent stimuli in the Stroop color-word interference task (Potenza et al. 2003a), during anticipation of gains and losses in the monetary incentive delay (MID) task (Balodis et al. 2012a; Choi et al. 2012), during a simulated gambling task (Reuter et al. 2005), and (in comorbid PG and SUDs) during performance of the Iowa Gambling Task (Tanabe et al. 2007). However, seemingly contradictory findings have also been reported. During high-risk gambling decisions in the Iowa Gambling Task (IGT), fMRI findings demonstrated that PG individuals exhibited relatively greater frontal lobe and basal ganglia activation, particularly in the vmPFC, caudate, and amygdala (Power et al. 2011). Differences in findings across studies may relate to the specific tasks used, populations studied, or other factors. Cue-induction studies have also reported both relatively decreased (Potenza et al. 2003b) and increased (Crockford et al. 2005; Goudriaan et al. 2010) vmPFC activity for problem/PG (versus control) in response to gambling stimuli. Taken together, dysfunction in frontal areas appears to contribute to PG, although the precise nature of the dysfunction is unclear.

Dysfunction in the striatum may also contribute to PG. Decreased ventral striatal activation to reward anticipation in the MID task (Balodis et al. 2012a) and during simulated gambling (Reuter et al. 2005) has been reported among PG. In gambling cue-exposure tasks, PG exhibited decreased activation in the ventral (Potenza 2008) and dorsal (de Greck et al. 2010) striatum compared to controls. These findings are consistent with reward anticipation studies among individuals with substance addictions (Hommer et al. 2011; Wrase et al. 2007). In both PG and alcohol dependence, ventral striatal activation during reward anticipation was inversely correlated with impulsivity measures (Balodis et al. 2012a; Beck et al. 2009). Moreover, both ventral striatal and vmPFC activation were inversely correlated with severity of gambling symptomatology in PG subjects such that greater severity of PG was associated with lower ventral striatal and vmPFC activity during simulated gambling (Reuter et al. 2005).

Aside from frontal and striatal circuits, other brain regions have also been implicated. PG (versus controls) displayed significantly greater activity in the right parahippocampal gyrus and left occipital cortex, including the fusiform gyrus, to video presentation of gambling cues (Crockford et al. 2005). Among PG, subjective intensities of gambling urges following viewing of gambling videos correlated positively with activation in brain regions implicated in the retrieval and processing of emotion including the bilateral temporal poles, medial temporal gyrus, and medial occipital gyrus and inversely with activation in the left dorsal medial frontal cortex, an area involved in performance monitoring; control participants did not show gambling-urge-related correlations at the same threshold (Balodis et al. 2012b). Relatively diminished insula activation in PG during reward processing has also been noted (Balodis et al. 2012a).

Neuroanatomical alterations may also exist in PG. Diffusion tensor imaging (DTI) findings suggest reduced fractional anisotropy (FA) values in regions

including the corpus callosum in PG compared to control subjects (Joutsa et al. 2011; Yip et al. 2013). In addition, multiple regression analyses suggest that this reduction is significantly predicted by PG status as well as age and past alcohol abuse/dependence (Yip et al. 2013). To our knowledge, only two voxel-based morphometry (VBM) studies have been conducted among individuals with PG. Both studies report no volumetric differences in gray and white matter between PG and control subjects (Joutsa et al. 2011; van Holst et al. 2012).

90.2.1.2 Neurochemistry

Dopaminergic findings in PG present a complicated picture. Using positron emission tomography (PET) with the tracer [^{11}C]raclopride, a recent study reported that not only did PG perform worse on the IGT than controls, among PG, dopamine release in the ventral striatum was positively associated with excitement levels (Linnet et al. 2011). Increased dopamine levels may serve a "double deficit" function by reinforcing PG behavior through increasing excitement levels while simultaneously reducing inhibition of risky decisions. D2/D3 receptor availability has also been shown to negatively correlate with mood-related impulsivity ("urgency") within the striatum (Clark et al. 2012) and positively correlate with problem-gambling severity within the dorsal striatum (Boileau et al. 2013) among PG. However, unlike findings in substance addiction literature (Volkow et al. 2001), no significant difference in D2/D3 receptor availability at resting state was observed between PG and control subjects (Boileau et al. 2013; Clark et al. 2012; Linnet et al. 2011). However, a between-group difference in ventral striatum dopamine D2-like receptor availability and dopamine release has been reported in individuals with Parkinson's disease (Steeves et al. 2009). While there were no differences in the magnitude of dopamine release between PG and controls during a slot machine gambling task, among PG, dopamine release correlated positively with problem-gambling severity (Joutsa et al. 2012). Dopamine agonists have been associated with impulse control disorders in Parkinson's disease (Leeman et al. 2012). Further, oral administration of a D2-like receptor antagonist, haloperidol, increased gambling motivations among PG subjects, while no such effect was observed among controls (Zack and Poulos 2007), although individual differences appear to be important (Tremblay et al. 2011). Individual differences may explain with the lack of efficacy of D2-like antagonist drugs (e.g., olanzapine) in the treatment of PG (Fong et al. 2008; Grant and Potenza 2004; McElroy et al. 2008). Taken together, these data suggest a role for dopamine in PG, but one that may include within-group individual differences.

Pharmacological studies also implicate serotonin in PG. Selective serotonin reuptake inhibitors (SSRIs) have had mixed results for PG and substance addictions (Potenza et al. 2009). For example, some randomized control trials have found fluvoxamine and paroxetine to be superior to placebo in treatment of PG (Hollander et al. 2000; Kim et al. 2002), while others have reported negative findings (Blanco et al. 2002; Grant et al. 2003). Heterogeneity in treatment response may result from individual differences, with some data suggesting that individuals with co-occurring anxiety disorders may respond well to SSRIs (Bullock and Potenza 2012).

Other neurotransmitter systems may also contribute to PG. Dysregulated hypothalamic-pituitary-adrenal (HPA) axis and increased noradrenergic levels have been observed in PG (Meyer et al. 2004). Opioid antagonists (e.g., naltrexone and nalmefene) have demonstrated superiority over placebo in multiple randomized clinical trials (Bullock and Potenza 2012; Grant et al. 2010b; Kim et al. 2001). Following a 6-month open-label naltrexone treatment, the majority of PG patients did not relapse during a 6-month medication-free follow-up (Dannon et al. 2007). Thus, opioid antagonist treatment may have lasting effects, although controlled trials with longer-term follow-up are needed to examine this possibility. Lithium and the glutamatergic nutraceutical n-acetyl cysteine have also shown promise in small controlled trials (Bullock and Potenza 2012). Memantine, an N-methyl D-aspartate (NMDA)-type glutamate receptor antagonist, reduced both the number of hours spent gambling per week and money spent gambling in PG after 10 weeks of medication; in addition, PG subjects reported improved cognitive flexibility posttreatment suggesting that glutamate may contribute to impulsive and compulsive behaviors (Grant et al. 2010a).

90.2.1.3 Genetics/Family History

Data from the Vietnam Era Twin Registry estimate the heritability of PG to be 50–60 % (Lobo and Kennedy 2009; Shah et al. 2005). This estimate is similar to those from substance addictions (Kreek et al. 2005). Twin studies suggest that genetic factors may contribute more than environmental factors to the overall variance of risk for developing of PG (Blanco et al. 2012; Slutske et al. 2010).

Genetic polymorphisms related to dopamine transmission (e.g., *DRD2* and Taq1A1) (Comings et al. 1996; Lobo et al. 2010) and serotonin transmission (e.g., *5HTTLPR* and *MAO-A*) (de Castro et al. 1999; Ibanez et al. 2000) have been associated with PG, albeit not in a consistent fashion. These genes may have addictive effects (Comings et al. 2001). However, genetic studies are best considered preliminary given the small sample sizes and absence of stratification by demographics. Replication of candidate gene studies using alternate designs is needed. Towards this end, a recent genome-wide association study was performed but did not identify single-nucleotide polymorphisms (SNPs) reaching genome-wide significance (Lind et al. 2012).

90.2.1.4 Conclusion

PG has been the most frequently studied behavioral addiction and is the most likely to be reclassified from an Impulse Control Disorder (ICD) to the proposed *DSM-5* category, "Addiction and Related Disorders" (American Psychiatric Association 2012). Although the neurobiology of PG is incompletely understood, recent neuroimaging, neurocognitive, neurochemical, and genetic work indicate similarities with SUDs (Leeman and Potenza 2012).

90.2.2 Internet Addiction Disorder

The Internet is integrated firmly into modern society and has radically changed the way we conduct our daily lives. Its popularity, particularly among youth, has raised

concern over its potential harms. While moderate Internet use may enhance one's quality of life by widening social circles and enhancing psychological well-being (Chen et al. 2002; Willoughby 2008), diminished control over Internet use may impact negatively on daily function, family relationships, physical and mental health, and may lead to incarceration and legal troubles (Anderson 2000; Ko et al. 2012; Sanders et al. 2000; Willoughby 2008). While no formal diagnostic criteria for "Internet addiction disorder" (IAD) or problematic Internet use currently exist in the DSM, the condition may involve excessive or poorly controlled urges and a maladaptive obsession with the Internet (Ko et al. 2012). Definitions of IAD are often based on *DSM-IV-TR* criteria for pathological gambling (Dowling and Quirk 2009; Ko et al. 2009b; Young 1999) with some, such as Young's Internet Addiction Scale, having demonstrated sufficient reliability (Bernardi and Pallanti 2009; Widyanto and McMurran 2004). In terms of comorbidity, IAD may frequently co-occur with not only SUDs (Bai et al. 2001; Lam et al. 2009; Yen et al. 2009) but also various psychiatric conditions including impulse control, mood, and personality disorders (Bernardi and Pallanti 2009; Dowling and Brown 2010; Dowling and Quirk 2009; Mazhari 2012).

90.2.2.1 Neural Systems

Electrophysiological studies indicate diminished efficiency of response inhibition in IAD. Recordings of the P3 amplitude, an event-related potential (ERP) associated with response evaluation and inhibitory processing, were found to be higher and have longer peak latency among IAD (versus controls) during a Go/No Go task (Dong et al. 2010). These findings suggest IAD individuals may need to engage more cognitive resources to inhibit behavior and are less efficient in information processing. Another study by the same research group found that for incongruent conditions during the Stroop task, IAD (versus controls) showed reduced medial frontal negativity (MRN), suggesting impaired cognitive control (Dong et al. 2011b). These findings resemble those from SUDs (Garavan and Stout 2005; McGue et al. 2001).

A recent fMRI study reported that IAD (versus control) demonstrated greater activation in the anterior and posterior cingulate cortices for incongruent conditions during the Stroop task (Dong et al. 2012). Moreover, greater anterior cingulate cortex (ACC) activation was associated with slower incongruent reaction time and more severe scores on Young's Internet Addiction Scale across all participants (Dong et al. 2012). In a guessing task with monetary gain and losses, increased activation of the orbitofrontal cortex (OFC) to gain trials and decreased ACC in loss trials was observed in IAD compared to controls suggesting sensitization to reward and desensitization to loss (Dong et al. 2011a). Resting-state abnormalities in IAD subjects have also been detected with increased regional homogeneity observed in the right frontal region, left superior frontal gyrus, right cingulate gyrus, bilateral parahippocampus, and other regions (Liu et al. 2010). Increased regional homogeneity may reflect enhancement of synchronization among these regions which may consequently enhance sensitivity to rewards.

Evidence also indicates potential structural differences. Using MRI, lower gray matter density in regions tied to emotion regulation including the ACC, posterior cingulate cortex, insula, and lingual gyrus has been found (Zhou et al. 2011). Moreover, gray matter volumes of the right dorsolateral prefrontal cortex (dlPFC), left ACC, the right supplementary motor area, and white matter FA measures in the posterior limb of the internal capsule have been negatively correlated with the duration of IAD (Yuan et al. 2011).

In the same study, Yuan et al. (2011) also reported increased FA within the region of the left internal capsule accompanied by decreased FA within the right parahippocampal gyrus among IAD adolescents. This finding appears to contrast with results from Lin et al. (2012) who reported widespread reduction of FA in major white matter pathways and abnormal white matter structure in IAD adolescents. Taken together, these data suggest involvement of white matter microstructures in the pathophysiology of IAD, although the precise relationship warrants further research.

90.2.2.2 Neurochemistry

Several small studies have explored dopaminergic functioning in IAD. A recent study using single-photon emission computed tomography (SPECT) scans reported decreased striatal dopamine transporter expression among male IAD subjects compared to age-matched controls (Hou et al. 2012). In addition, the authors reported significantly decreased volume of the bilateral corpus striatum among IAD subjects. Another study using [^{11}C]raclopride (PET) scanning reported that adult males with IAD (versus male controls) had reduced dopamine D2-like receptor availability in subdivisions of the striatum including the bilateral dorsal caudate and left dorsal putamen compared to controls; moreover, receptor availability was negatively correlated with IAD severity (Kim et al. 2011). Interestingly, dopamine receptor availability in the ventral striatum did not differ between the control and IAD groups (Kim et al. 2011), contrasting results from SUDs (Dalley et al. 2007; Heinz et al. 2004). Further studies are needed regarding the role of dopamine in IAD.

90.2.2.3 Genetics/Family History

Few studies have investigated genetics underlying IAD. Homozygosity of the short allelic variant of the *5HTTLPR* (*SS-5HTTLPR*) gene may be more frequent among male IAD adolescents (Lee et al. 2008). IAD subjects expressing *SS-5HTTLPR* showed higher harm avoidance and scored higher on Young's Internet Addiction Scale than IAD individuals who expressed other variants of the gene (Lee et al. 2008). The nicotinic acetylcholine receptor subunit alpha 4 (CHRNA4) gene may also contribute to IAD. The T-variant (CC genotype) of the rs1044396 polymorphism on the CHRNA4 gene occurred more frequently among IAD (versus control) subjects; further analyses revealed that this finding was driven by females, suggesting sex-specific genetic effects (Montag et al. 2012).

90.2.2.4 Conclusion

IAD is a behavioral addiction that may be increasingly prevalent concurrent with increased Internet availability, accessibility, and popularity. Although the neurobiology of IAD remains under-researched, recent years have shown promising progress. It is important to note that most studies have targeted adolescent males and have been performed in Asia; therefore, results may not be generalizable to other populations. IAD was proposed for inclusion in Sect. III, a part of the *DSM-5* in which conditions that require further research are located. 'Internet Gaming Disorder' has been included in Sect. III and has been flagged as a possible candidate for future inclusions in the addictions category. However, criteria for this condition are currently limited to Internet gaming and does not include Internet use for other purposes including for online gambling, or social media.

90.2.3 Problematic Video-Game Playing

Similar to IAD, problematic video-game playing (PVG) or "video-game addiction" is not currently described in the *DSM* (although Internet Gaming Disorder has been included in Sect. III), and assessment tools are often based on the *DSM-IV-TR* definitions for PG (e.g., Tejeiro et al. 2002). Some have argued that PVG is a subtype of IAD, and both should be considered under the umbrella term pathological technology use (Sim et al. 2012). However, it is important to consider the two conditions individually as each may be associated with different clinical and health-related correlates (Yau et al. 2012). PVG may be both similar to and distinct from other behavioral addictions such as PG and IAD in terms of availability and use of visual and auditory rewards – and such differences may contribute to PVG's unique features (Griffiths 2002; Sussman et al. 2011). However, research on PVG often does not differentiate between online and off-line games, making it difficult to separate PVG from IAD findings.

90.2.3.1 Neural Systems

Electrophysiological data indicate reduced frontal-central error-related negativity (ERN) amplitudes among PVG (versus controls) in response to incorrect trials relative to correct trials in the Go/No Go task, suggesting compromised error processing among PVG subjects (Littel et al. 2012). In addition, ERN amplitude was negatively correlated with weekly gaming hours (Littel et al. 2012). This finding parallels those from SUDs (Franken et al. 2007; Sokhadze et al. 2008) and suggests that individuals engaged in either behavior may be desensitized to negative consequences.

In one of the largest imaging studies on PVG to date, Kühn et al. (2011) conducted MRI scans on 154 14-year olds and found both functional and structural differences between frequent ($\geq$9 h/week) and infrequent ($<$9 h/week) video-game players. In the MID task, frequent players showed greater activation of the ventral striatum during loss feedback compared with no loss. Moreover, higher left striatal gray matter volume was observed among frequent compared to infrequent players, and this volumetric difference was found to negatively correlate with deliberation

time on the Cambridge Gambling Task (CGT). Striatal differences have also been noted in cue-induction studies. Post-cue changes indicative of increased activity have been found in the right NAc and right caudate nucleus among male adults playing >30 h/week on the "World of Warcraft" game compared to "non-heavy" gamers playing <2 h/week (Ko et al. 2009a).

In addition to striatal findings, Ko et al. (2009) also reported greater activation in the right OFC, bilateral ACC, medial frontal cortex, and right dlPFC in heavy (versus non-heavy) players following cue presentation. Activation of these areas was positively correlated with self-reported gaming urge and recall of gaming experience provoked by "World of Warcraft" pictures (Ko et al. 2009a). Similar findings have been reported in subsequent studies examining individuals with current PVG (Han et al. 2010b; Sun et al. 2012) and those in remission from online PVG (Ko et al. 2011). Healthy male adults who played a novel video game for 60 min per day for 10 days showed stronger activation of the left inferior frontal gyrus, left parahippocampal gyrus, bilateral parietal lobes, thalamus, and right cerebellum in response to video-game stimuli compared to neutral-control stimuli (Han et al. 2011). Activation of the right medial frontal lobe and right parahippocampal gyrus also positively correlated with gaming urge (Han et al. 2011).

90.2.3.2 Neurochemistry

In an early neurobiological study of video-game playing using [^{11}C]raclopride (PET) scanning, increased release of dopamine to D2-like receptors in the ventral striatum was observed following 50 min of video-game playing in healthy adult males (Koepp et al. 1998). A more recent study using SPECT similarly suggested increased dopamine release in the caudate during a motorbike racing computer game, compared to baseline measures among healthy adult males (Weinstein 2010). While video-game playing may be capable of inducing dopamine release that is comparable to the effects of psychoactive substances (Farde et al. 1992; Volkow et al. 1994), the role of dopamine dysfunction in PVG is unclear, and to date, no study has directly investigated a relationship.

Following a 6-week trial of bupropion (a drug with influences on dopaminergic and other neurotransmitter systems), individuals with online PVG (>30 h StarCraft/week) demonstrated decreased craving for video-game play, reduced total game play time, and less cue-induced brain activity in the dlPFC compared to pretreatment (Han et al. 2010a).

90.2.3.3 Genetics/Family History

Genetic studies for PVG are very limited, and to our knowledge, only one study has been conducted. Han et al. (2007) reported that the presence of the Taq1A1 allele of *DRD2* and the low activity Val158Met variant of COMT genes were more prevalent among online PVG adolescent males than controls.

90.2.3.4 Conclusion

Despite public attention, PVG remains understudied, and findings are often difficult to compare between studies given the use of different measures across studies.

However, preliminary studies suggest neurobiological similarities with substance addictions, particularly with respect to ventral striatal structure and function.

90.2.4 Hypersexual Disorder

Although "hypersexual disorder" or "sexual addiction" was considered for inclusion in the *DSM-5*, it was ultimately not accepted. It may be defined as recurrent or repetitive compulsive sexual behavior. It is primary conceptualized as a nonparaphilic sexual desire disorder with impulsivity and/or compulsivity components (Fong 2006; Kafta 2010). Some individuals who suffer from hypersexual disorder may display clinical features that resemble addictive disorders including craving prior to behavioral engagement, impaired control over behavioral engagement, and behavioral engagement despite adverse consequences (Kor et al. 2013), while other individuals may present symptoms resembling ICD or obsessive-compulsive disorders (OCD) (Gold and Heffner 1998).

90.2.4.1 Neural Systems

To our knowledge, only one neuroimaging study in hypersexual disorder exists. Using DTI, Miner et al. (2009) found that although mean diffusivity in the inferior frontal region was negatively correlated with impulsivity, FA and mean diffusivity measures of this area did not differ between hypersexual disorder patients and controls. These data suggest possible differences from other behavioral addictions in which associations with inferior frontal white matter disorganization have been reported (i.e., low FA and high mean diffusivity), albeit not always in inferior frontal regions (Grant et al. 2006; Joutsa et al. 2012; Yip et al. 2013; Yuan et al. 2011). Further research is needed to investigate neuroanatomical differences associated with hypersexual disorder.

Evidence from animal research suggests that the medial prefrontal cortex (mPFC) contributes to sexual behaviors. mPFC lesions in rats block the acquisition of sex-aversion condition and impair the suppression of seeking of sexual rewards in the face of aversive consequences (Davis et al. 2010). Whether activity of the mPFC and other frontal areas plays a role in hypersexual disorder remains to be studied.

90.2.4.2 Neurochemistry

Our current understanding of the neurochemistry of hypersexual disorder is predominantly derived from pharmacological studies. In a double-blind, placebo control study of hypersexual disorder in homosexual and bisexual men, the selective serotonin reuptake inhibitor (SSRI) citalopram was found to reduce sexual desire without lessening sexual satisfaction (Wainberg et al. 2006). Another SSRI, fluoxetine, was found effective in reducing symptoms in men with either paraphilia or paraphilia-related disorders (Kafka and Hennen 2000). In addition, better results were obtained when methylphenidate was used in conjunction with fluoxetine, suggesting an additive effect and implicating possible involvement of dopamine and norepinephrine (Kafka and Hennen 2000).

Naltrexone, an opioid receptor antagonist, appears effective in treating hypersexual disorder. Administration of high doses (100–200 mg/day) has been reported to successfully reduce hypersexual disorder symptoms, sexual urges, sexual fantasies, and masturbation in two case report studies (Grant and Kim 2001; Raymond et al. 2002). These features, however, recurred following naltrexone discontinuation (Grant and Kim 2001).

Other investigators have suggested that medications (such as SSRIs and lithium) do not specifically manage sexually addictive behaviors but rather treat comorbid psychiatric disorders which in turn help patients become more accessible to their hypersexual disorder issues (Sealy 1995). Controlled trials and systematic studies are needed to fully examine the efficacies and tolerabilities of medications for hypersexual disorder.

90.2.4.3 Genetics/Family History

Limited findings suggest individuals suffering from hypersexual disorder were more likely to have parents with a similar condition and were more likely to have a first-degree relative with SUDs (Schneider and Schneider 1996). Carnes (1998) reported that 87 % of hypersexual disorder patients come from a family with addiction problems.

90.2.4.4 Conclusion

Hypersexual disorder is a serious clinical condition that can have detrimental effects on daily life. Neurobiological research in hypersexual disorder, particularly with respect to neuroanatomical and neurocircuitry data, is currently very limited.

90.2.5 Food Addiction

Food addiction has been discussed in the popular media and has received some research attention. Addictive processes have been suggested to underlie obesity (Volkow and O'Brien 2007). Emerging neurobiological research suggests both substance use and eating behaviors engage similar neurocircuitry and has consequently led to the conceptualization of "foods as drugs" (Davis and Carter 2009). However, the concept of food addiction remains debated with some investigators arguing that existing research has yielded conflicting results (Ziauddeen et al. 2012a, b) and others arguing that this construct may be particularly relevant to certain subgroups of obese individuals, such as those with binge eating disorder (BED) (Avena et al. 2012; Gearhardt et al. 2011a). Although not labeled as such, several core features of BED share similarities with those for substance dependence including strong food cravings and diminished control over eating (Gearhardt et al. 2011a). Over a quarter of clinicians report often or always using addiction-based therapies for BED (von Ranson and Robinson 2006), further suggesting clinical and phenomenological similarities. It is important to note that for some individuals, overeating is a relatively passive event that takes the form of liberal snacking, eating large portions, and physical inactivity (Avena et al. 2011; Marcus and Wildes 2009), and the extent to which these behaviors constitute an addiction may be debated. Individuals with food addiction may be more impulsive, display

greater emotional reactivity and food cravings than obese individuals without food addiction (Davis et al. 2011), and thus have clinically relevant features associated with food addiction.

90.2.5.1 Neural Systems

Imaging studies in obese (versus lean) subjects have documented significantly increased activation of the vmPFC and dlPFC upon exposure to food-related stimuli (Gautier et al. 2000; Miller et al. 2007). Other prefrontal areas (such as the OFC and cingulate gyrus) have been implicated in feeding motivations (Rolls 2004). Moreover, obese individuals (versus controls) showed greater activation in regions associated with cue-related craving for substance addictions including the ACC, striatum, insula, and dlPFC in response to pictures of high-calorie food versus low-calorie food (Rothemund et al. 2007; Stice et al. 2009; Stoeckel et al. 2008). Healthy adults placed under a nutritionally adequate but monotonous diet, compared to those on an unrestricted diet, showed greater activation of the hippocampus, insula, and caudate in response to cues of foods they favored (Pelchat et al. 2004). Obese versus lean individuals have also shown enhanced corticolimbic-striatal activation to favorite-food cues and stress cues in a guided imagery fMRI task (Jastreboff et al. 2013). In the same study, measures of insulin resistance correlated positively with regional brain activations to favorite-food, stress, and neutral-relaxing cues in obese but not lean individuals, and regional brain activations (particularly in the thalamus) mediated the relationships between insulin resistance and favorite-food-cue-induced craving in obese but not lean individuals. These data suggest that obese individuals may be hyperresponsive to food cues (particularly those of high-caloric value) and that metabolic measures may relate to these brain activations differently in obese and lean individuals.

While cue-induction studies suggest increased activation in regions involved in the reward system among obese people, ingestion of food has been associated with reduced activation of the brain reward system. Stice et al. (2008) found that obese (versus lean) adolescent girls showed diminished caudate nucleus activation in response to anticipated intake and actual consumption of palatable food intake. The authors suggest that this may potentially reflect decreased dopamine receptor availability. Downregulation of the dopaminergic mesolimbic system may motivate overeating to temporarily compensate for an under-stimulated reward system and may ultimately lead to food addiction.

Obesity is a heterogeneous construct and emerging evidence suggests that certain subgroups, such as those with BED, may exhibit food addiction features more so than others. Individuals with BED compared to BMI-matched non-BED obese and lean individuals showed relatively diminished activity in the vmPFC, inferior frontal gyrus, and insula during the Stroop task (Balodis et al. 2013). The same research group found that during a MID task, BED obese individuals showed relatively diminished ventral striatal activity during anticipatory phases relative to non-BED obese individuals, whereas non-BED obese individuals showed heightened ventral striatal and vmPFC responses compared to lean

individuals (Balodis et al. 2013). Taken together, these results suggest that neural differences exist between obesity subgroups.

To our knowledge, only one neuroimaging study has directly assessed food addiction. Gearhardt et al. (2011b) found that activation in the ACC, medial orbitofrontal cortex, and amygdala in response to anticipated receipt of food was positively correlated with food addiction scores among lean and obese young females. Furthermore, females with high food addiction scores, compared to those with low scores, showed decreased activation in the OFC during food intake. No significant correlation was observed between food addiction score and BMI, suggesting that food addiction and related neural functioning may occur among individuals with a range of body weights.

90.2.5.2 Neurochemistry

Dopamine release has been related to food and food cues (Di Chiara and Imperato 1988). Administration of dopamine antagonists can abolish the responding for food in rats (Wise and Rompre 1989). Development of addiction-like reward deficits and onset of compulsive-like food seeking was accelerated by lentivirus-mediated knockdown of striatal D2-like receptor in rats with extended access to palatable, high-fat food (Johnson and Kenny 2010). Studies using [^{11}C]raclopride (PET) scanning have demonstrated that D2-like receptor availability is reduced in obese individuals (Wang et al. 2009) and mice (Geiger et al. 2008; Huang et al. 2006). Moreover, among obese individuals, D2-like receptor availability correlated negatively with body mass index (BMI) scores (Wang et al. 2001).

Data from animal models suggest ingestion of foods of different palatability, and energy density produces different effects in the dopaminergic system. Rats classified as prone to binge eating consumed significantly more highly palatable and energy-dense (high fat, high sugar) food and tolerated higher levels of foot-shock for such foods than binge eating-resistant rats (Oswald et al. 2011). Regular consumption of energy-dense food may have lasting consequences on the brain. Using a diet-induced model of obesity, rats fed a high-sugar diet compared to those on an unrestricted diet showed decreased dopamine release in the NAc following 36 h of food deprivation (Avena et al. 2008). Similarly, Alsiö et al. (2010) found that rats fed a high-fat (versus unrestricted) diet showed decreased expression of D1 and D2 receptors in the VTA, NAc, and PFC following an 18-day withdrawal. Furthermore, obesity-prone rats showed increased craving and anxiety compared to obesity-resistant rats during the second withdrawal week following discontinuation of the energy-dense diet (Pickering et al. 2009). Future studies are needed to examine whether these dietary findings extend to human subjects.

The serotonin and norepinephrine reuptake inhibitors sibutramine and SSRI fluoxetine have shown some efficacy in treating eating disorders and are approved by the Food and Drug Administration for treatment of obesity and bulimia nervosa, respectively, although the former has been recalled in the United States for cardiovascular safety concerns (McElroy et al. 2012). SSRIs in general have been shown to be effective in targeting binge eating, psychiatric, and weight symptoms (Reas and Grilo 2008), although the effectiveness and duration of these medications

remain under debate. Open-label studies report initial SSRI (citalopram and fluoxetine) administration reduced binge eating and weight loss in BED patients; at a 6-month follow-up, these beneficial effects were maintained with continuation of SSRI treatment (Leombruni et al. 2006, 2008). In a randomized, double-blind, 12-week study of escitalopram for the treatment of individuals with co-occurring BED and obesity, individuals receiving high-dose escitalopram treatment had significantly greater reductions in weight, BMI, frequency of binge episodes, and global severity of illness scores than those receiving placebo treatment (Guerdjikova et al. 2008). Fluoxetine treatment for BED significantly increased the odds of binge abstinence immediately posttreatment; however, these effects may not be long-lasting as no significant improvement in BED symptoms was observed during the 29-month follow-up despite improvements in depressive symptoms (Devlin et al. 2007).

Opioids are implicated in eating behavior (Kelley et al. 2002), although the precise nature of their influences are unclear. High doses of the opiate antagonist, naloxone, increased sugar consumption and opiate-like withdrawal symptoms including elevated plus-maze anxiety, teeth chattering, and head shakes in sugar-binging rats following a period of abstinence (Avena et al. 2008, 2009; Colantuoni et al. 2002). These findings may, however, be unique to sugar binging. A recent study by Bocarsly et al. (2011) reported that rats on high-fat diets did not show signs of opiate-like withdrawal when exposed to naloxone. Taken together, these findings suggest that the brain opioid system may be differently affected by the overeating of different nutrients.

90.2.5.3 Genetics/Family History

Obesity is tenfold more likely in people with an obese first-degree relative (Segal and Allison 2002). When pregnant rats maintained a highly palatable and energy-dense (high fat, high sugar) diet, their offspring showed an increased preference for sugar and fat in comparison to those with mothers on a control diet (Vucetic et al. 2010). Additionally, dopamine and opioid receptor expression was increased in reward-related brain regions including the NAc, PFC, and hypothalamus (Vucetic et al. 2010). In humans, obese individuals with BED, in contrast to non-BED obese controls, had lower frequencies of the Taq1A1 allele of the *DRD2* gene and higher frequencies of the G118 allele of the mu-opioid receptor gene (*OPRM1*) (Davis et al. 2009). Taken together, genetic data suggest dopamine and opioid receptor genotypes may be involved in obesity and different patterns of eating. Genetic polymorphism of the *5HTTLPR* has also been implicated. S allele carriers showed higher BMI scores than homozygous LL carriers and were more frequent among overweight adolescents (Sookoian et al. 2007).

90.2.5.4 Conclusion

Unlike some behavioral addictions, eating behaviors have been tested extensively using animal models, and a considerable amount of neurobiological research has been generated. Data suggest that animal results may be transferable to human

populations, although further research is needed. Certain subgroups of people with obesity (e.g., those with BED) and certain diets (e.g., highly palatable, energy dense) may share more neurobiological similarities with SUDs. Such findings have important implications, and the extent to which a food addiction model applies to individuals with obesity and its subgroups merits further consideration.

90.2.6 Compulsive Shopping Disorder

Classically referred to as "oniomania," compulsive shopping disorder (CSD) has had a long-standing history (in comparison to more recent phenomena such as IAD and PVG) and was clinically described a century ago by German psychiatrist Emil Kraepelin (1915). Interest in CSD has rekindled in recent years with work conducted by consumer behaviorists (see review: Black 2007).

90.2.6.1 Neural Systems

A recent fMRI study found stronger NAc activity among compulsive shoppers (versus controls) during the initial product presentation phase of a multiphase purchasing task (Raab et al. 2011). During a subsequent price presentation phase, compulsive shoppers showed reduced activation of the insula and ACC. ACC activity was also higher among compulsive shoppers during the concluding decision phase. To our knowledge, this is currently the only neuroimaging study on compulsive shopping.

90.2.6.2 Neurochemistry

Beneficial results of citalopram, an SSRI, have been reported in a small 12-week open-label trial, and in a 6-month follow-up, CSD patients continuing citalopram were less likely to relapse than those who discontinued the medication (Koran et al. 2002). A subsequent study found those assigned placebo were more likely to relapse compared to those randomized to continue taking citalopram in a 9-week double-blind, placebo-controlled administration following a 7-week open-label trial (Koran et al. 2003). Further research is needed to understand the effects of citalopram discontinuation.

Findings from other SSRIs have been negative. Another study by Koran et al. (2007) found no difference between escitalopram and placebo conditions. Double-blind comparisons of fluvoxamine and placebo similarly found no difference in compulsive shopping symptom reduction (Black et al. 2000; Ninan et al. 2000). As such, further research is needed prior to the clinical utilization of SSRIs for compulsive shopping.

90.2.6.3 Genetics/Family History

There is some evidence that suggests compulsive shopping runs in families. Of 18 individuals with CSD, three had one or more first-degree relative with CSD, and 11 had relatives with an SUD (McElroy et al. 1994). Negative findings have been reported for *5HTTLPR* polymorphisms (Devor et al. 1999).

90.2.6.4 Conclusion

Our current knowledge of the neurobiology and genetics of CSD is limited, but preliminary research suggested altered neurofunctional responses to shopping stimuli. Further research is needed to determine the role of various neurotransmitters, the efficacy of different medications, and the underlying biology of the disorder.

90.3 Conclusion

Research in behavioral addictions is challenging due to the heterogeneity of the behaviors, with certain subgroups arguably fitting better in an addiction framework than others (Grant et al. 2010c). Further complications stem from the arguably normative nature of these behaviors which has caused disagreements among researchers as to what constitutes an addiction (Avena et al. 2012; Block 2008; Yau et al. 2012). Uniformly agreed-upon diagnostic criteria and assessment tools will not only facilitate comparisons across studies but may help to ensure that cutoff points are appropriately generated. Additional research in the domains of neuroimaging, neurochemistry, genetics, and treatment is needed to increase knowledge of behavioral addictions to the level of that for substance addictions. In particular, future studies investigating often underrepresented female populations (especially for IAD and PVG) and studies conducted longitudinally would provide valuable information and more comprehensive understandings.

Keeping these limitations in mind, existing research suggests parallels between behavioral addictions and SUDs. Data are most extensive for PG, and there is sufficient evidence to warrant considering it as a non-substance or behavioral addiction. Although many gaps in knowledge remain, research in IAD, PVG, hypersexual disorder, food addiction, and CSD has accelerated in recent years, with early work yielding promising results. Other behaviors not discussed in this review such as kleptomania, trichotillomania, skin-picking, and intermittent explosive disorder may also merit consideration as behavioral addictions, although few neurobiological studies have investigated these behaviors. In the current state of knowledge, it seems premature to classify all impulse control disorders in the proposed addiction category in the upcoming *DSM-5*.

Neuroscientific approaches to addiction have traditionally been based on the premise that addiction is a process that results from brain changes associated with chronic intake of physical substances. Although the neurobiologies of behavioral addictions remain relatively poorly understood, recent research suggests that prolonged and pathological engagement in addictive behaviors may lead to neuroadaptations and structural changes in ways similar to psychotropic drugs and/or that similar biological features may lead to the development of behavioral and substance addictions. Given the considerable co-occurrences of behavioral and substance addictions, an improved understanding of their relationships has important implications for not only furthering our understanding of the neurobiology of both sets of disorders but also improving prevention and treatment strategies.

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The Psychological Underpinnings of Addictive Behaviours

91

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Contents

Abstract

Conceptualizing, diagnosing, and treating behavioral or process addictions (addictions to nondrug activities, such as gambling, sex, Internet use and gaming, eating, shopping, work, and exercise) have proven to be conceptually complex. As a means of addressing this complexity, we adopt a syndrome model of addiction, which views the disorder of addiction as a syndrome with multiple opportunistic expressions and multiple, interacting biological, psychological, and experiential elements. In this chapter we refine our focus to how the psychological factors of impairment of control, craving, motives and

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expectancies, and personality influence the addiction syndrome of excessive behaviors. We draw upon relevant research on these psychological factors as they relate to excessive behaviors, integrate these findings, and propose implications for treating excessive behaviors. A transdiagnostic treatment approach is suggested that recognizes the dynamic interaction between personality characteristics, emotional and cognitive states, interpersonal problems, and excessive behaviors but also uses a tailored case conceptualization to identify the optimal specific treatment focus and approach as relevant to specific individuals and types of behavioral problems.

91.1 Introduction

The notion of behavioral or process addictions, or addictions to nondrug activities, such as gambling, sex, Internet use and gaming, eating, shopping, work, and exercise, is conceptually complex. There is a lack of consensus with regard to labels, criteria, and conceptualization (Mudry et al. 2011). Researchers and practitioners view behavioral addictions from a variety of perspectives: as an impulse control disorder, a compulsive-impulsive spectrum disorder, a disorder of impaired control, a pathological disorder, or an addiction/dependence (Blaszczynski and Nower 2002; Cantinotti et al. 2009; Grant and Potenza 2005).

An addiction disorder can be broadly conceptualized as requiring the following criteria: (a) craving and compulsion, (b) loss of control, and (c) continuing the behavior despite experiencing adverse consequences (Zuckerman 2012). Addiction is not just a label or diagnosis but a dynamic process; those afflicted by addiction have been seen to go through phases of exacerbation and abstention, with episodes of controlled activity (Shaffer 2012). This addiction process is more about a relationship process than about the object, substance, or behavior. Shaffer argues:

> the most common conceptual error committed by clinicians, researchers, and public policymakers is to think that addiction resides as a latent property of an object (i.e., a drug or game of chance) . . . When a particular pattern of behaviour can reliably and robustly change emotional experience in a desirable way, the potential for addiction emerges. The relationship of the addicted person with the object of that person's excessive behaviour – not just the attributes of the object – is what defines addiction. (p. xxxii)

91.2 A Syndrome Model of Addiction

New lines of research have reconsidered addiction as a complex pattern of activity, using a syndrome model of addiction, which we adopt in our conceptualization of behavioral addiction. A syndrome model of addiction (Shaffer et al. 2004) views the disorder of addiction as a syndrome with multiple opportunistic expressions and multiple, interacting biological, psychological, and experiential elements. The addiction syndrome has unique and shared components: unique components manifest as a specific expression of the addiction syndrome as reflected by particular objects

(e.g., cigarettes, slot machines), whereas shared components manifest as common sequelae among various expressions of the addiction syndrome (e.g., depression, deception) (Shaffer et al. 2004). Addiction also has shared neurobiological and psychosocial antecedents and shared experiences (e.g., manifestations and sequelae). Research has shown that various addictions have shared manifestations, parallel natural histories, object nonspecificity (not linked to a particular substance or behavior), concurrent manifestations, and treatment nonspecificity (Shaffer 2012).

According to the syndrome model of addiction, antecedents of the addiction syndrome include individual vulnerability levels, object or behavioral exposure, and interaction. Throughout their lives, people encounter and accumulate specific interactions of neurobiological and psychosocial elements that can influence their behavior. While some elements increase the likelihood of addiction, others have protective mechanisms. Similarly, individuals are exposed to, and have access to, different behaviors and objects, over their life, increasing an individual's likelihood towards excessively engaging in one behavior over another.

When at-risk individuals interact with a particular behavior, they may experience neurobiological consequences that are both common to all types of addiction (e.g., activation of reward circuitry) and also unique to specific behaviors (e.g., psychoactivity) (Shaffer et al. 2004). After repeated engagement in a particular behavior, the neurobiological and/or social consequences of these interactions produce a desirable (or sought-after) subjective shift that is reliable and robust, creating a premorbid stage of the addiction syndrome. Here, people teeter on a delicate balance that can shift them towards an addiction process.

The addiction syndrome can be recursive, its sequelae generating a new vulnerability profile (e.g., provoking reward-system malfunction in a previously normal system). The addiction syndrome itself places individuals with the syndrome at increased risk for continuing addictive behavior and for developing new addictive behaviors. This chain of events is evident in the addiction syndrome, via parallel natural histories of different manifestations of addiction, including relapse patterns, addiction hopping, treatment nonspecificity, and addiction comorbidity.

Some psychosocial antecedents that appear to be relevant are the psychological factors of the individual who is engaging in behaviors excessively. In the remainder of this chapter, we examine the psychological factors that may influence the development and perpetuation of the addiction syndrome. Specifically, we review how the psychological factors of impairment of control, craving, motives and expectancies, and personality influence the addiction syndrome of excessive behaviors.

91.2.1 Impairment of Control and Craving

According to the DSM-IV, the essential feature of impulse control disorders such as pathological gambling is the failure to resist an impulse, drive, or temptation to perform an act that is harmful to an individual (American Psychiatric Association 2000). This description contains features that are similar to the central attributes of our common conceptions of addiction – some degree of impairment of control over

the addictive behavior as well as continuing involvement despite the emergence of negative consequences (Goodman 1990). The concepts of impulse dyscontrol and impairment of control are comprised of both behavioral and psychological aspects. In terms of behavior, the individual engages in the behavior despite a decision to abstain or limit involvement. The addicted drinker drinks much more than intended in an evening and drinks more days than he planned in the week, the addicted gambler returns to the casino despite vowing to stay away, and the compulsive shopper seeks credit at yet another online store breaking a commitment to family members not to go online again. Impairment of control is reflected behaviorally in failure of self-control.

The psychological aspect of impairment of control is typified by an impulse, temptation, urge, or craving that precedes the behavior and intensifies when the individual stops or cuts back their involvement. The addicted smoker experiences a craving for a cigarette shortly after getting up in the morning. The addicted video gamer feels a strong urge to get back to the computer throughout a family celebratory dinner.

Impairment of control and craving are long-recognized concepts in the alcohol and substance dependence field, with an extensive literature available. Although the concepts are ultimately clinically useful, both have been criticized for their unclear, and perhaps flawed, conceptual underpinnings. Impairment of control, for example, has been described as a tautology – it is seen as both evidence of addiction and as resulting from addiction (Eiser 1990). It is used both to describe addiction and to explain addiction (Table 91.1).

The concept of craving is also conceptually fuzzy. Rosenberg (2009) points out that definitions of alcohol and other drug craving may include multiple "response domains" including emotional experiences (e.g., desire, irritability, anxiety), cognitive effects (e.g., intrusive thoughts), physiological experiences (e.g., heart rate, respiration, salivation), and overt behaviors (e.g., seeking alcohol). These domains may, or may not, covary within the individual. Moreover, craving is sometimes viewed as an enduring background state (indicating overall severity of addiction) and sometimes as transient and episodic (influenced by a variety of situational factors). Most definitions describe craving as a subjective experience, although some also describe craving as potentially occurring outside of conscious awareness (Sayette et al. 2000).

Notwithstanding these conceptual issues, a variety of reliable and valid measures of impairment of control and craving have been developed (Marsh et al. 2002; Rosenberg 2009). Advancements in the ability to measure craving, in fact, influenced the proposal by the DSM-5 working committee to add craving to the list of diagnostic criteria for substance addiction (O'Brien 2011). Recent research has also shown that craving is a consistent indicator of alcohol problems cross-culturally, which supports its addition to the DSM criteria set. Cherpitel and colleagues (2010) reported that craving was a mid severity indicator in emergency room samples in four diverse drinking cultures (Poland, Mexico, Argentina, United States). Research on the craving and impairment of control concepts with other behavioral addictions is less advanced.

Table 91.1 Psychological underpinnings

Behavior	Summary points
Impairment of control (IoC)	
Problem gambling (PG)	IoC has been described as a core feature of PG distinguishing between heavy and problematic involvement
	DSM-IV criteria included repeated unsuccessful efforts to control, cut back, or stop gambling
	IoC has been associated with attentional bias to gambling cues, chasing gambling losses, and avoidance style of coping
	Negative affect and alcohol increased IoC within gambling sessions
Sexual behavior (SB)	IoC has been described as a diagnostic feature of excessive SB, although there is little empirical research
	The "dual control" model proposed that "out of control" SB, including masturbation and sexual relationships, results from sexual arousal occurring during periods of negative mood and low inhibition of response
Internet and gaming	IoC is proposed as a core feature to distinguish frequent from problematic involvement
	Studies have identified correlates of impaired control over gaming, including impulsivity, low self-esteem, lower academic performance, and insecure attachment
	No gaming or Internet-specific IoC assessment tool has been described, although a number of related "addiction" scales include individual loss of control items
Shopping	Concepts such as "failure of self-control," "low levels of effortful control," and "failure of self-regulation" appear to capture a phenomenon similar to IoC
Eating	The term "dietary restraint" is frequently used in eating disorders and low restraint suggests lack of control
	IoC in eating has been described as a natural adaptation to food deprivation and low weight
Craving	
Problem gambling (PG)	A number of studies illustrate importance of craving, in particular its predictive validity of relapse and recovery after treatment and persistence after gambling losses
	Imaging studies have used gambling cues to assess the neurocircuitries associated with cravings, generally common with substance addictions
	Self-reported craving may be greater for gambling in pathological gamblers than drinking among alcoholics
	Craving severity has been shown to decrease with use of naltrexone in treatment efficacy studies
	Well-validated self-report scales of craving have been developed
Sexual behavior (SB)	Craving is infrequently investigated, although sexual urges are considered part of the phenomenology of compulsive SB
	A small literature of treatment of sexual addictions include an open-label trial of naltrexone that reduced cravings

(*continued*)

Table 91.1 (continued)

Behavior	Summary points
Internet and gaming	Similar to gambling-related craving, craving has been correlated with both positive and negative affect when individuals were engaged in the activity but only negative affect when prevented from playing
	The neurocircuitry associated with gaming craving is similar to gambling and substance abuse
	An open-label trial of bupropion has reported a decrease in craving
Eating	In behavioral and imaging studies, craving is elicited by exposure to food cues, and degree of reactivity is predictive of binge eating in women
	While the neurocircuitry seems similar to substance abuse craving, whether craving for food is qualitatively similar to craving in other addictions is controversial, as is the conceptualization of compulsive overeating as an addiction
Expectancies	
Problem gambling (PG)	Those with PG are more likely to endorse both positive (enjoyment/arousal, self-enhancement, money) and negative expectancies (over-involvement, emotional impact) relative to non-gamblers, social gamblers, and at-risk gamblers. Both expectancies with respect to gambling outcomes – especially affective types of expectancies – are associated with gambling frequency and gambling-related problems
Sexual behavior (SB)	Whereas one study demonstrated strong associations between expectancies and sexual practices, other studies found weak or no associations. This may be due to the notion that the potential costs and benefits of sexual behavior vary considerably depending on particular individuals and circumstances
Internet and gaming	In one study both positive and negative Internet use expectancies were positively correlated with an addiction measure
	In a second study, the Internet gaming addiction group held greater levels of implicit positive expectancies
Eating	Relatively more rigorous research has been applied to eating disorders. Positive expectancies for eating have differentiated bulimia nervosa from anorexia nervosa patients, normal controls, and psychiatric controls
	Longitudinally, thinness/restricting and eating expectancies predicted the subsequent onset of binge eating and purging behavior among adolescent girls
	Compared to a psychoeducational intervention, a thinness expectancy manipulation intervention produced greater declines in thinness expectancies, body dissatisfaction, and overall eating-disordered attitudes
Motives	
Problem gambling (PG)	At least two gambling motives questionnaires have been developed: a five-factor model (socialization, amusement, avoidance, excitement, and monetary motives) and a three-factor model (enhancement, coping, and social motives). Both have been used to demonstrate associations between gambling motives and gambling frequency and severity
	Researchers have demonstrated that relative to social and enhancement gamblers, coping gamblers scored higher on a variety of different gambling activities and problems and even scored higher on drinking frequency, problems, and coping motives – suggesting consistency of motives across addictive behaviors

(*continued*)

Table 91.1 (continued)

Behavior	Summary points
Sexual behavior (SB)	A four-factor model has been proposed, where sex is used to enhance physical or emotional pleasure (enhancement motives), cope with threats to self-esteem or to minimize negative emotions (coping motives), bond with a socially significant other (intimacy motives), and avoid disapproval by a socially significant other (peer/partner approval motives)
	Intimacy and enhancement motives were strongly associated with positive feelings about sex, more frequent intercourse, and higher levels of satisfaction. Coping and peer/partner approval motives were associated with negative responses to sex, low levels of sexual satisfaction, decreased frequency of sex, and thoughts to lead to riskier, more maladaptive SB
Internet and gaming	One study found that males were more likely than females to score higher on a measure of online gaming addiction and to be endorsed in playing online games to pursue feelings of achievement and make social contacts
	A second study reported that the motives of substitution (a ritualized orientation to fill time, relax, and escape), information seeking, and social interaction were related to Internet use dependency
	Another study highlighted motives related to being lonely and using the Internet to relieve psychosocial problems
Eating	A four-factor model has been applied to eating disorders including coping, social, compliance, and pleasure motives. Each motive was found to be associated with a unique pattern of eating behavior: coping and compliance motives were positively associated with restrictive eating, bingeing, and purging; pleasure motives were positively associated with binge eating, were negatively associated with restrictive eating, and were unrelated to purging; and social motives were negatively associated with restrictive eating and purging but positively associated with bingeing
	Eating-disordered groups have been found to endorse drinking coping motives, suggesting consilience of motives across addictive disorders
Shopping	One consumer marketing study identified seven shopping motives (three functional motives – safety, bargain hunting, convenience – and four hedonic motives: entertainment, freedom, appreciation of modernity, self-identity). Another consumer marketing study identified six hedonic shopping motives (adventure, gratification, role, value, social, idea). The gratification motive resembles the construct of coping motives (shopping for stress relief and mood alteration)
	Other researchers have posited a cognitive-behavioral model of compulsive buying, whereby they allude to more clinically based research suggesting that the primary motivation for compulsive buying is mood alteration
Exercise	Two literatures on excessive exercise have been proposed: one that examines exercise motives in the context of eating-disordered individuals and one that examines exercise motives among nonclinical samples
	Using an exercise motivation questionnaire, researchers found five factors (telic/planning, telic/serious, paratelic, mastery, sympathy), more highly endorsed among regular exercisers versus non-regular exercisers
	Several studies investigated excessive exercise motives among eating-disordered populations with four factors: weight/appearance, fitness/health, mood regulation, and socializing. Eating-disordered patients were more likely to endorse excessively exercising for body weight and shape

(*continued*)

Table 91.1 (continued)

Behavior	Summary points
	reasons as compared to healthy women; and among adult female excessive exercisers receiving inpatient treatment for eating disorders, reduced eating disorder was correlated with a reduction in perceived importance of exercise to regulate negative affect but not with importance of exercise for weight/appearance (these associations were not found in non-excessive exercisers)
Work	One research group has applied self-determination theory to excessive work to derive two primary motives: controlled motivation (working for external and internal rewards and avoiding punishments) versus autonomous motivation (working for personal importance of an activity and interest). Autonomous motivation was positively associated with excessive work, whereas controlled motivation was positively associated with compulsive work
Personality	
Problem gambling (PG)	Across the models researchers have found high levels of impulsivity to be most commonly associated with PG
	Researchers have demonstrated the relevance of low conscientiousness, low openness to experience, low agreeableness, high levels of neuroticism, elevated levels of novelty seeking, both risk-taking and harm avoidance, and lower levels of self-directedness and cooperativeness
	There may be different subtypes of gamblers based on personality characteristics
Sexual behavior (SB)	There is a paucity of research
	Examining the related personality characteristics, one clinical case study utilized Carnes' "Master of the Universe" conceptualization to explain the narcissistic nature of the sexualized addictive personality
	Neuroticism (experiencing and difficulty regulating negative affect) was found to be a predictor of hypersexual behavior
Internet and gaming	Researchers have demonstrated a range of traits as potentially relevant: low self-directedness, lower reward dependence, high novelty seeking, high sensation seeking, high harm avoidance, high neuroticism, high state and trait anxiety, high aggression, low agreeableness, low extraversion, low self-control, low conscientiousness, and narcissistic personality traits
Eating	Few studies examined personality traits related to eating, and those available have focused on binge eating and obesity
	Overweight and obese individuals with binge-eating symptoms scored higher on impulsivity
	Obese persons were more likely to score high in novelty seeking and low in self-directedness
	Women who either binge eat or abuse alcohol exhibited a high degree of impulsivity and endorsed socially deviant attitudes ("externalizers"). Women with both addictive behaviors were not impulsive or socially deviant, but manifested a high degree of emotional instability ("neuroticism"), and might be considered "internalizers"
Shopping	Compulsive buying has been associated with impulsivity, novelty seeking, narcissism, and materialism

(*continued*)

Table 91.1 (continued)

Behavior	Summary points
	"Buying addiction" has been associated with emotional distress (anxiety, depression, and obsessive-compulsiveness), the presence of specific personal qualities (low conscientiousness, low self-esteem, external locus of control, and sensation seeking), and the tendency to escape from or avoid stress produced in daily life
	Impulsive buying is related to extraversion (positive affectivity, sensation seeking); compulsive buying is related to neuroticism (emotional instability, negative affect). Both have been related to lack of self-regulation or effortful control
Work	Associations have been found between workaholism and narcissism, conscientiousness, extraversion, openness to experience, agreeableness, and neuroticism
	Different personality dimensions seem to be related to different aspects of the work construct (work involvement, work drive, and work enjoyment). Work involvement was positively associated with conscientiousness, agreeableness, extraversion, and openness to experience. Work enjoyment has been positively associated with agreeableness, conscientiousness, extraversion, and openness to experience and negatively associated with neuroticism. While conscientiousness and neuroticism were positively related to work drive, agreeableness was negatively associated with work drive, and openness to experience had contradictory associations with work drive
	Somewhat contradictory personality characteristics lend support for subtypes of "workaholics." "Enthusiastic workaholics" are highly involved with work, driven by internal pressure to work, and find great pleasure in doing so. "Non-enthusiastic workaholics" are also highly involved and driven to work-related activities but seem not to derive enjoyment from it
Exercise	Excessive exercise has been associated with high harm avoidance, high persistence, high extraversion, high neuroticism, low self-directness, less mature character, and low agreeableness
	Individuals with high neuroticism could be using exercise as a coping strategy for their stress or be using exercise to address excessive worry or concern over their appearance/health. Upbeat, energetic (extraverted) individuals may be drawn to exercise, and individuals who are low in agreeableness tend to be egocentric and competitive
Multiple areas	Few researchers have examined personality traits common to or differentiating between multiple addictive behaviors
	In comparing bulimia nervosa and PG, researchers have found high novelty seeking to be specifically associated with a diagnosis of problem gambling and low self-directedness to be associated with both bulimia nervosa and PG. Women with both bulimia nervosa and PG displayed higher harm avoidance and cooperativeness than control women, whereas men with problem gambling reported higher reward dependence and persistence than control men, highlighting potential differences between sexes
	Two studies examined compulsive buying and eating disorders. Reward sensitivity and cognitive anxiety have been positively related to excessive eating and compulsive buying. Impulsivity was positively related to compulsive buying, whereas somatic anxiety and social desirability were negatively related

(*continued*)

Table 91.1 (continued)

Behavior	Summary points
	Compulsive buying could be more impulsivity driven, whereas eating disorder symptoms (especially drive for thinness) might be more anxiety related
	In a study examining personality factors related to substance use, gambling, and computer gaming, high impulsivity was the only personality characteristic associated with all addictive behaviors

91.2.1.1 Impairment of Control

In terms of behavioral addictions, the impaired control concept from the substance addiction area has been mostly adopted in the gambling addiction realm. Blaszczynski and Nower (2002), for example, described impaired control as a necessary and core feature of gambling disorders that distinguishes heavy gambling involvement from problematic involvement. The concept is also captured in one of the DSM-IV diagnostic criteria for pathological gambling: repeated unsuccessful efforts to control, cut back, or stop gambling (American Psychiatric Association 2000). At the same time, concerns about the conceptualization of impairment of control in the gambling field, as in the substance abuse field, have been raised with the recommendation that the concept needs to be more clearly operationalized (Cantinotti et al. 2009).

Much of the early descriptive work on impairment of control was conducted by Dickerson and colleagues in Australia, examining electronic gambling machines and other forms of gambling (Dickerson and O'Connor 2006). This research demonstrated that impairment of control seems similar across different types of gambling (O'Connor and Dickerson 2003) and was associated with attentional bias to gambling cues (Boyer and Dickerson 2003), chasing gambling losses (O'Connor and Dickerson 2003), and avoidance style coping with problems (Shepherd and Dickerson 2001). Both negative affect, such as depression and frustration (Dickerson 1993), and alcohol (Baron and Dickerson 1999) increased impairment of control within gambling sessions. Dickerson and colleagues also developed the only gambling-specific measure of impaired control (Corless and Dickerson 2006; O'Connor and Dickerson 2003).

In the sexual behavior area, scholars who use an addiction conceptualization describe impairment of control as a diagnostic feature (e.g., Goodman 2001; Mick and Hollander 2006; Orford 1978), although little empirical research has been reported (Garcia and Thibaut 2010). A "dual control" model proposes that sexual arousal depends upon a balance between arousal and inhibition of sexual response. The model proposes that "out of control" sexual behavior, including masturbation and sexual relationships, results from sexual arousal occurring during periods of negative mood and low inhibition of response (Bancroft 2008). An assessment tool based upon this model has been developed with the hope of promoting empirical investigation (Bancroft et al. 2009).

Impairment of control is also proposed as an essential feature of gaming and Internet addiction to distinguish frequent from problematic involvement

(Charlton and Danforth 2007; Griffiths 2000; Meerkerk et al. 2010; Wood and Griffiths 2007). A qualitative study of online gamers in treatment found that participants described losing control as an important marker of the development of their problem (Beranuy et al. 2013). A number of studies have identified correlates of impaired control over gaming, including impulsivity (Meerkerk et al. 2010) and low self-esteem (Armstrong et al. 2000). Impaired control defined as "refusal self-efficacy" (i.e., lack of confidence in one's ability to refuse involvement) was linked to impulsivity, lower academic performance, insecure attachment, and male gender in Taiwanese college students (Lin et al. 2011). No gaming or Internet-specific impairment of control assessment tool has been described, although a number of Internet and gaming "addiction" scales include individual loss of control items (e.g., Yen et al. 2009; Young 1998).

Although the impairment of control construct is not used in the compulsive shopping and buying literature, concepts such as "failure of self-control" (Baumeister 2002), "low levels of effortful control" (Claes et al. 2010), and "failure of self-regulation" (Peters and Bodkin 2007) appear to capture a similar phenomenon. Similarly, the term "dietary restraint" is frequently used in the eating disorder literature and low restraint suggests lack of control. Impaired control in eating has been described as a natural adaptation to food deprivation and low weight. The difference of this concept from drugs and alcohol is that the desire to eat is biologically adaptive and successful recovery requires a reduction of dietary restraint (Wardle 2011).

91.2.1.2 Craving

The craving construct has also been utilized in conjunction with a number of behavioral addictions. In the area of gambling, a recent review of research on assessment of craving uncovered a number of studies that illustrate the importance of craving as an element of gambling disorders (Ashrafioun and Rosenberg 2012), in particular its predictive validity of relapse and recovery after treatment (Cantinotti et al. 2007; Hodgins and el-Guebaly 2004; Ladouceur et al. 2007; Smith et al. 2010) and persistence after gambling losses (Young and Wohl 2009). A number of imaging studies have used gambling cues to assess the neurocircuitries associated with cravings in gambling disorders (e.g., Crockford et al. 2005; Goudriaan et al. 2010; van Holst et al. 2010), and results generally show commonalities with substance abuse addictions (Mudry et al. 2011). Two studies directly compared self-reports of craving from alcoholics and pathological gamblers and found that the intensity of craving was greater for gambling (de Castro et al. 2007; Tavares et al. 2005). Craving has been shown to be associated with psychosocial stress (Elman et al. 2010) and gambling advertising (Binde 2009), but, unexpectedly, not with attentional bias to gambling cues (Brevers et al. 2011). Craving severity has also been shown to decrease with use of naltrexone in treatment efficacy studies (e.g., Kim et al. 2001; Walther et al. 2012).

In their review, Ashrafioun and Rosenberg (2012) identified a number of well-validated self-report scales of craving in gambling, as well as indirect measures

such as physiological reactivity that had been used in substance abuse craving research. Beyond the gambling area, specific measures of craving have not been developed for other behavioral addictions, although some research exists.

The literature on craving in Internet and video gaming is smaller than gambling but seems to be developing along similar lines. A qualitative study of online gaming addicts receiving treatment found that craving is an indicator of problem development (Beranuy et al. 2013). A recent study of 160 gamers involved in massive multiplayer online role-playing games concluded that gaming shows the same emotional pattern as gambling-related craving. Craving correlated with both positive and negative affect when individuals were engaged in the activity but only negative affect when prevented from playing (Stoeber et al. 2011). From a neurobiological perspective, imaging studies have suggested that the neurocircuitry associated with gaming craving is similar to gambling and substance abuse (Han et al. 2010b; Ko et al. 2009, 2011). An open-label trial has demonstrated a decrease in craving associated with administration of bupropion, an antidepressant used for smoking and other addictions (Han et al. 2010a).

The concept of craving has been infrequently investigated in the area of sexual behavior although sexual urges are considered part of the phenomenology of compulsive sexual behavior (e.g., Coleman 1992; Goodman 2001). Fong (2006) reviewed a small literature of treatment of sexual addictions, including an open-label trial of naltrexone that reduced cravings (Ryback 2004). In the eating literature, the effect of food cues has been investigated in a number of behavioral and imaging studies. For example, it has been shown that craving is elicited by exposure to food cues, and degree of reactivity is predictive of binge eating in women, although perhaps not men (Sobik et al. 2005). Similarly, in imaging studies in other behavioral addictions, the neurocircuitry involved seems similar to substance abuse craving (Pelchat et al. 2004). However, whether craving for food is qualitatively similar to craving in other addictions is controversial, as is the conceptualization of compulsive overeating as an addiction more broadly (Davis and Carter 2009; Liu et al. 2010; Wardle 2011; Wilson 1991, 2010).

91.2.2 Expectancies and Motives

Expectancies and motives are two closely linked, albeit distinct social-cognitive constructs. They were first heavily researched in the alcohol literature as determinants of alcohol use and problematic drinking and have since been applied to other substances and addictive behaviors. Whereas expectancies refer to an individual's belief regarding the effects or outcome of a particular substance or addictive behavior, motives refer to an individual's reasons for using a particular substance or engaging in a particular addictive behavior (Cooper 1994; Goldman et al. 2006).

Cox and Klinger (1988) first articulated the relationship between expectancies and motives in their motivation model for alcohol use. According to their model, drinking behavior is embedded in historical (e.g., genetic disposition), personality (e.g., extraversion, sensation seeking), sociocultural (e.g., drinking styles),

environmental (e.g., alcohol availability), and situational (e.g., reinforcement from recent drinking) factors, as well as alcohol expectancies and drinking motives (Kuntsche et al. 2007). Motives are thought to be more proximal than expectancies and are regarded as the gateway through which more distal influences, such as expectancies, are mediated (Cooper et al. 1995; Kuntsche et al. 2007). In the alcohol literature, environmental influences (both familial and individual-specific) have been found to shape expectancies, while heritable influences have been suggested to predispose motives (Agrawal et al. 2008). As might be expected, the relationship between expectancies and motives has received less empirical attention in the area of behavioral addictions.

91.2.2.1 Expectancies

There is a rich literature providing empirical evidence for the explanatory role of alcohol expectancies in the variation of drinking patterns, whereby among both adolescents and adults, alcohol expectancies have been found to have moderate to strong associations with drinking (Goldman et al. 2006). Typically, positive expectancies (e.g., beliefs that positive feelings will be enhanced and negative feelings will be reduced) have been found to be related to initiation and early consumption of alcohol use, whereas negative expectancies (e.g., beliefs that negative consequences will occur) have been found to be related to reduction and cessation of alcohol use (Jones et al. 2001).

While research into the etiology and maintenance of behavioral addictions is relatively new compared to substance-related addictions, the concept of expectancy has been applied to gambling (e.g., Gillespie et al. 2007; Shead et al. 2008; Walters and Contri 1998; Wickwire et al. 2010), sexual behavior (e.g., Gilbert et al. 1986; Katz et al. 2000; Lavery et al. 1993), Internet and gaming addiction (e.g., Lin et al. 2008; Yen et al. 2011), and eating disorders (e.g., Annus et al. 2008; Hohlstein et al. 1998; Smith et al. 2007). To our knowledge, not a single study has investigated expectancies in the context of shopping, exercise, or work, which clearly points to the need for future research in these areas.

In the area of gambling, Gillespie and colleagues (2007) have developed a Gambling Expectancy Questionnaire (GEQ) that taps five distinct outcome expectancy constructs: three related to positive expectancies (enjoyment/arousal, self-enhancement, and money) and two related to negative expectancies (over-involvement and emotional impact). Using the GEQ, the authors found that probable pathological gamblers were more likely to endorse both positive and negative expectancies relative to non-gamblers, social gamblers, and at-risk gamblers. Similar findings have been reported demonstrating that positive and negative expectancies with respect to gambling outcomes – especially affective types of expectancies – are associated with gambling frequency and gambling-related problems (e.g., Shead et al. 2008; Walters and Contri 1998; Wickwire et al. 2010).

The small expectancy literature in the area of sexual behavior has been equivocal. Whereas one study demonstrated strong associations between expectancies and sexual practices (Gilbert et al. 1986), other studies have found weak or no associations (Katz et al. 2000; Lavery et al. 1993). Katz and colleagues speculate

that one reason for the weak or no associations observed might be due to the notion that the potential costs and benefits of sexual behavior vary considerably depending on particular individuals and circumstances (e.g., the potential consequences associated with having unprotected sex with a monogamous partner differ from those associated with having unprotected sex with a stranger).

Two studies based in Taiwan have examined the expectancy construct with respect to Internet and gaming addiction. In the first study, both positive and negative Internet use expectancies were significantly and positively correlated with an Internet addiction measure among college students (Lin et al. 2008). In the second study, young adults with Internet gaming addiction reacted faster in an implicit association task to congruent pairing of Internet gaming screenshots and liked words compared to control participants, thereby suggesting that the Internet gaming addiction group held greater levels of implicit positive expectancies for Internet gaming (termed by the authors as positive motivational implicit responses) (Yen et al. 2011).

Compared to other behavioral addictions, relatively more rigorous research with respect to expectancies has been applied to eating disorders. For example, positive expectancies for eating have been found to differentiate bulimia nervosa patients from anorexia nervosa patients, normal controls, and psychiatric controls (Hohlstein et al. 1998). Longitudinally, thinness/restricting and eating expectancies have been found to predict the subsequent onset of binge eating and purging behavior among adolescent girls (Smith et al. 2007). Moreover, compared to a psychoeducational intervention, a thinness expectancy manipulation intervention has been found to produce greater declines in thinness expectancies, body dissatisfaction, and overall eating-disordered attitudes, thereby providing further support for the role of expectancies in the etiology of eating-disordered behaviors (Annus et al. 2008).

91.2.2.2 Motives

Motives have been described as more proximal and diagnostic than expectancies (Cooper 1994). Following Cox and Klinger's (1988) motivational model, Cooper (1994) first proposed a framework of motives, whereby motives are characterized by valence (positive vs. negative) and source (internally generated vs. externally generated). The result of this framework produced a four-factor model of drinking motives: drinking to obtain social rewards (social motives), drinking to enhance positive affect (enhancement motives), drinking to cope with negative affect (coping motives), and drinking to avoid social rejection (conformity motives). Originally, Cooper and colleagues demonstrated differential associations between drinking motives and alcohol use behavior; for example, social and enhancement motives were found to be related to heavy drinking and to drinking in situations where heavy drinking is tolerated (such as at parties), whereas coping motives were found to be related to drinking in isolation (such as at bars) (Cooper 1994; Cooper et al. 1995). As with expectancies, a wealth of empirical research has since demonstrated that drinking motives are associated with and can predict alcohol use behavior, whereby in general, social motives appear to be associated with

moderate alcohol use, enhancement motives with heavy drinking, and coping motives with alcohol-related problems (Kuntsche et al. 2005; Schelleman-Offermans et al. 2011).

With respect to behavioral addictions, motives have been investigated in the context of gambling (e.g., Lee et al. 2007; Stewart and Zack 2008; Stewart et al. 2008), sexual behavior (e.g., Cooper et al. 1998, 2011), Internet and gaming addiction (e.g., Junghyun et al. 2009; Ko et al. 2005; Sun et al. 2008), eating disorders (e.g., Jackson et al. 2003; Luce et al. 2007), shopping (e.g., Arnold and Reynolds 2003; Farrag et al. 2010; Kellet and Bolton 2009), exercise (e.g., Bratland-Sanda et al. 2010; Cash et al. 1994; Keele 2009; Mond and Calogero 2009), and work (e.g., Van den Broeck et al. 2011).

Derived from Cooper's (1994) alcohol motives model, at least two gambling motives questionnaires have been developed: one is a five-factor model (socialization, amusement, avoidance, excitement, and monetary motives) (Lee et al. 2007) and the other is a three-factor model (enhancement, coping, and social motives) (Stewart and Zack 2008). Both questionnaires have been used to demonstrate associations between gambling motives and gambling frequency and severity. Moreover, Stewart and colleagues (2008) used their gambling motives questionnaire to demonstrate that relative to social and enhancement gamblers, coping gamblers scored higher on a variety of different gambling activities and gambling problems and even scored higher on drinking frequency, drinking problems, and drinking coping motives, thereby supporting an empirical approach to subtyping gamblers based on motives and suggesting consistency of motives across addictive behaviors.

Shortly after Cooper (1994) developed her alcohol motives model, the framework was applied to the area of sexual behavior in the form of a four-factor model: having sex to enhance physical or emotional pleasure (enhancement motives), having sex to cope with threats to self-esteem or to minimize negative emotions (coping motives), having sex to bond with a socially significant other (intimacy motives), and having sex to avoid disapproval by a socially significant other (peer/partner approval motives) (Cooper et al. 1998). This model has been used to demonstrate that both intimacy and enhancement motives were strongly associated with positive feelings about sex, more frequent intercourse, and higher levels of satisfaction. Coping and peer/partner approval motives were associated with negative responses to sex, low levels of sexual satisfaction, and decreased frequency of sex and are thought to lead to riskier and more maladaptive sexual behavior (Cooper et al. 2011).

Although not explicitly derived from Cooper's (1994) alcohol motives model, the concept of motives has been investigated in the area of Internet and gaming addiction. For example, one study found that among Taiwanese adolescents, males were more likely than females to score higher on a measure of online gaming addiction and were more likely to endorse playing online games for reasons to pursue feelings of achievement and make social contacts (Ko et al. 2005). Another study reported that among American adults, the motives of substitution (a ritualized orientation to fill time, relax, and escape), information seeking, and social

interaction were related to a measure of Internet use dependency (Sun et al. 2008). Consistent with the construct of coping motives, yet another study reported that among American undergraduate students, motives related to being lonely and using the Internet to relieve psychosocial problems were associated with measures of compulsive Internet use and negative outcomes (Junghyun et al. 2009).

Cooper's (1994) alcohol motives model has been specifically applied to eating disorders, whereby a four-factor model yielding the following motives has been developed and validated: coping, social, compliance, and pleasure motives (Jackson et al. 2003). Each motive was found to be associated with a unique pattern of eating behavior, such that coping and compliance motives were positively associated with restrictive eating, bingeing, and purging; pleasure motives were positively associated with binge eating, were negatively associated with restrictive eating, and were unrelated to purging; and social motives were negatively associated with restrictive eating and purging but were positively associated with bingeing. As in the gambling motives literature, the relationship between eating disorders and drinking motives has also been investigated, whereby eating-disordered groups have been found to endorse drinking coping motives (Luce et al. 2007), suggesting consilience of motives across addictive disorders.

While Cooper's (1994) alcohol motives model has not yet been explicitly applied to the area of shopping, motives for shopping have been investigated in a rather piecemeal fashion in two related but distinct literatures: clinical research that examines shopping addiction versus consumer marketing research. For example, one consumer marketing study using an Egyptian sample identified seven main shopping motives (three functional motives, safety, bargain hunting, and convenience; and four hedonic motives, entertainment, freedom, appreciation of modernity, and self-identity) (Farrag et al. 2010), whereas another consumer marketing study identified six hedonic shopping motives (adventure, gratification, role, value, social, idea) (Arnold and Reynolds 2003). While these two studies did not attempt to link motives with shopping-related problems or addiction, it is noteworthy that the gratification motive in Arnold and Reynolds' (2003) study resembles the construct of coping motives, as it describes shopping for reasons of stress relief and to alleviate negative mood. Indeed, Kellet and Bolton (2009) have posited a cognitive-behavioral model of compulsive buying, whereby they allude to more clinically based research suggesting that the primary motivation for compulsive buying is mood alteration.

As with the shopping motives literature, a perusal of the exercise motives literature also reveals a schism between two literatures: one that examines exercise motives in the context of eating-disordered individuals and one that examines exercise motives among nonclinical samples. For example, Keele (2009) developed an exercise motivation questionnaire with Mexican American adults in the general population and discovered five factors (telic/planning, telic/serious, paratelic, mastery, sympathy), all of which were more highly endorsed among regular exercisers versus non-regular exercisers. In contrast, several studies have investigated excessive exercise motives among eating-disordered populations and have employed a modified Reasons for Exercise Inventory (Cash et al. 1994) with four factors that are reminiscent of Cooper's (1994) model: weight/appearance, fitness/health, mood

regulation, and socializing. For example, Mond and Calogero (2009) found that eating-disordered patients were more likely to endorse excessively exercising for body weight and shape reasons as compared to healthy women; and Bratland-Sanda et al. (2010) found that among adult female excessive exercisers receiving inpatient treatment for eating disorders, reduced eating disorder psychopathology was correlated with a reduction in perceived importance of exercise to regulate negative affect, but not with importance of exercise for weight/appearance (these associations were not found in non-excessive exercisers).

Finally, to our knowledge, only one research group has investigated motives in the context of excessive or compulsive work (see Van den Broeck et al. 2011). This line of research has applied self-determination theory (Deci and Ryan 2000) to derive two primary motives: controlled motivation (working for external and internal rewards and avoiding punishments) versus autonomous motivation (working for personal importance of an activity and interest). In one of their studies, the researchers found that autonomous motivation was positively associated with excessive work, whereas controlled motivation was positively associated with compulsive work (Van den Broeck et al. 2011).

91.2.3 Personality

The notion of an "addictive personality" suggests that a particular personality profile may yield a greater propensity for an individual to develop an addiction. While early researchers have not found definitive evidence of an "addictive personality," scholars continue to attend to and measure the influence of personality traits on addictive behaviors. Personality is conceptualized and measured differently by researchers, and several attempts have been made to identify sets of traits that may encompass the full variety of human emotion, cognition, and behavior. The various models list factors necessary to explain individual variation, all of which may be accurate, though incongruent with one another, emphasizing aspects of personality. Personality trait theories have been popular among addiction researchers to explain and understand addictive behaviors.

Two common models used in addiction research are Cloninger's psychobiological personality model and the Five-Factor Model of Personality, also known as the "Big Five." Cloninger's psychobiological personality model (Cloninger 1987) and measure (the Temperament and Character Inventory, TCI) consists of four temperament dimensions (novelty seeking, harm avoidance, reward dependence, and persistence) and three acquired character dimensions (self-directedness, cooperativeness, and self-transcendence) (Cloninger et al. 1994). The Five-Factor Model of Personality identifies the following five factors as composing personality: extraversion, agreeableness, conscientiousness, emotional stability (vs. neuroticism), and openness to experience (Goldberg 1990). In general, there is a lack of robustness in findings relating to addictive behaviors and personality variables, as researchers often use different measures, variables, and small samples and yield findings that are sometimes inconsistent and even contradictory.

Research examining personality factors across behaviors remains sparse; however, research examining personality factors involved in specific behaviors is more common. Not surprisingly, gambling has had the longest history of study and has paved the way for such research. Across the various personality trait models, researchers have found high levels of impulsivity to be most common in those who gamble excessively (Benson et al. 2012; Chiu and Storm 2010; Forbush et al. 2008; Grall-Bronnec et al. 2012; Hwang et al. 2012; MacLaren et al. 2011; Myrseth et al. 2009; Reid et al. 2011; Tavares and Gentil 2007). Using the TCI, researchers have demonstrated that gamblers have elevated levels of novelty seeking and harm avoidance (Forbush et al. 2008; Nordin and Nylander 2007) and lower levels of self-directedness (Forbush et al. 2008; Janiri et al. 2007; Nordin and Nylander 2007) and cooperativeness (Forbush et al. 2008; Janiri et al. 2007). Using the five-factor model, researchers have demonstrated the relevance of low conscientiousness (Hwang et al. 2012; MacLaren et al. 2011), openness to experience (Hwang et al. 2012; Myrseth et al. 2009), and agreeableness (MacLaren et al. 2011) and high levels of neuroticism (MacLaren et al. 2011; Myrseth et al. 2009; Reid et al. 2011) or negative emotionality (King et al. 2010).

In a large-scale population-based American longitudinal study, Slutske and colleagues (2005) found problem gambling at age 21 years to be associated with higher levels of negative emotionality and with lower levels of constraint measured at age 18 years compared with control subjects. Problem gambling was also associated with risk-taking and impulsivity. These young adults were characterized by negative emotions such as nervousness or worry, anger, or aggressiveness; feeling mistreated or victimized; and unconstrained behaviors of risk-taking, impulsivity, and rebelliousness.

It may be the case that there are different subtypes of gamblers based on personality characteristics, which provides support for heterogeneity of problem gamblers. Alvarez-Moya and colleagues (2010) found four clusters of problem gamblers in Spain. Type I (disorganized and emotionally unstable) gamblers had schizotypic traits, high impulsiveness, substance and alcohol abuse, and early age of onset, as well as psychopathological disturbances (most severe gambling behavior). Type II (schizoid) gamblers showed high harm avoidance, social aloofness, and alcohol abuse. Type III (reward-sensitive) gamblers showed high sensation seeking and impulsiveness but no psychopathological impairments. Type IV (high functioning) showed a globally adaptive personality profile, low level of substance and alcohol abuse or smoking, and no psychopathological disturbances. Two of the types showed no impulsiveness or sensation seeking and one of them even exhibited good general functioning.

Similarly, in Canada, Vachon and Bagby (2009) found three clusters of gamblers: a simple subtype (with an absence of comorbidities); a "hedonic" subtype who were characterized by a strong attraction to excitement and pleasure (excitement seeking, positive emotions), as well as a tendency to be excitable and careless; and a "demoralized" subtype who were characterized by extreme negative affect (high neuroticism), impulsivity, low self-discipline, distrust, and poor motivation. This empirically based typology of gamblers is consistent with, and provides support for, Blaszczynski and Nower's (2002) "pathways model" of problem gambling.

There is a paucity of research examining the personality characteristics of individuals engaging in excessive sexual behavior. One clinical case study (Nixon and Theriault 2012) utilized Patrick Carnes' (1991) "Master of the Universe" conceptualization to explain the narcissistic nature of the sexualized addictive personality. In a larger American study, Reid and colleagues (2008) found neuroticism to be a strong predictor of hypersexual behavior; individuals who manifested symptoms of hypersexual behavior were more likely to experience negative affect (including alexithymia, depression, and vulnerability to stress) and deficits in regulating this affect.

Next to gambling, excessive engagement in online gaming or time on the Internet has been studied most. Although there is generally a lack of robustness in findings relating personality variables to Internet usage, researchers have demonstrated that certain personality traits may potentially play a role in excessive Internet use and gaming. Low self-directedness appears to be a predictor of problematic Internet use (Montag et al. 2011, 2010) and has been found to be a better predictor than neuroticism (Montag et al. 2010). Those engaging in excessive Internet use tend to score lower on reward dependence and higher on novelty seeking and harm avoidance than control subjects (Ko et al. 2006, 2010). Using the five-factor model, excessive Internet use has been positively correlated with high neuroticism (Charlton and Danforth 2010; Mehroof and Griffiths 2010; Peters and Malesky 2008; Tsai et al. 2009) and negatively correlated with agreeableness, extraversion, and conscientiousness (Peters and Malesky 2008).

Researchers have begun examining online gaming separate from and potentially different from excessive Internet use (no studies to date have compared the two in the domain of personality). Mehroof and Griffiths (2010) found five traits with significant associations with online gaming addiction among university students in the UK: neuroticism, sensation seeking, trait anxiety, state anxiety, and aggression. The strongest predictors were state anxiety and sensation seeking. Self-control had the least impact on online gaming addiction. While the findings regarding neuroticism, trait and state anxiety, and sensation seeking appear to fit in line with excessive Internet use, examining aggression is new to the literature. In South Korea, researchers have also found aggression and narcissistic personality traits to be positively correlated with online gaming addiction, with self-control negatively correlated (Kim et al. 2008).

Few studies have examined personality traits related eating or food addiction, and those available have focused on binge eating and obesity. Barry et al. (2009) found that overweight and obese individuals with binge-eating symptoms had high scores on a personality measure of impulsivity. Using the TCI, Sullivan and colleagues (2007) found that obese persons were more likely than normal weight individuals to have high novelty seeking scores and lower self-directedness scores. Comparing binge eating and alcohol abuse, Benjamin and Wulfert (2005) found women who either binge eat or abuse alcohol exhibited a high degree of impulsivity and endorsed socially deviant attitudes ("externalizers"). Women with both addictive behaviors were not particularly impulsive or socially deviant, but manifested a high degree of emotional instability ("neuroticism"), and might be considered "internalizers."

Just as Internet and online gaming have similarities and differences to gambling, so too does compulsive shopping or buying. Impulsivity (Black et al. 2012; Lejoyeux et al. 1997) and novelty seeking (Black et al. 2012) may be important in compulsive buying similar to other behaviors, as well as narcissism and materialism (Rose 2007). In a large Spanish study examining "buying addiction," Rodriguez-Villarino and colleagues (2006) found evidence for a connection between addictive buying and symptoms of emotional distress (anxiety, depression, and obsessive-compulsiveness), the presence of specific personal qualities (low conscientiousness, low self-esteem, external locus of control, and sensation seeking), and the tendency to escape from or avoid stress produced in daily life.

The tendency to use shopping as a means to escape stress or negative feelings may be a component of compulsive buying or a characteristic of a particular type of compulsive buying. In a small clinical sample in Germany, researchers found two distinct personality clusters (Mueller et al. 2010). The first cluster showed average scores on all the Big Five personality traits, whereas the participants in cluster II scored significantly higher on neuroticism and lower on the other four personality traits (negative scores on extraversion, openness, agreeableness, and conscientiousness). Subjects in cluster II showed higher severity of compulsive buying and a lower degree of control over compulsive buying symptoms and were more anxious, interpersonally sensitive, and impulsive.

Claes and Mueller (2011) found evidence to distinguish between impulsive and compulsive buying, based on personality traits of a nonclinical student sample. They argued that impulsive buying is related to extraversion (positive affectivity, sensation seeking), whereas compulsive buying is related to neuroticism (emotional instability, negative affect), with both impulsive buying and compulsive buying related to lack of conscientiousness (lack of self-regulation or effortful control).

Excessive engagement in work or "workaholism" is usually composed of three factors (work involvement, work drive, and work enjoyment) (Spence and Robbins 1992). Associations have been found between components of workaholism and narcissism (Andreassen et al. 2012; Clark et al. 2010), conscientiousness (Andreassen et al. 2010; Aziz and Tronzo 2011), extraversion (Andreassen et al. 2010; Burke et al. 2006), openness to experience (Andreassen et al. 2010; Aziz and Tronzo 2011; Burke et al. 2006), agreeableness (Andreassen et al. 2010; Aziz and Tronzo 2011), and neuroticism (Andreassen et al. 2010; Burke et al. 2006).

Different personality dimensions seem to be related to different aspects of the work construct. For example, conscientiousness (Aziz and Tronzo 2011), agreeableness (Aziz and Tronzo 2011; Andreassen et al. 2010), extraversion (Andreassen et al. 2010; Burke et al. 2006), and openness to experience (Andreassen et al. 2010) have been found to be positively associated with work involvement. Work enjoyment has been positively associated with agreeableness (Aziz and Tronzo 2011), conscientiousness (Aziz and Tronzo 2011), extraversion (Andreassen et al. 2010; Burke et al. 2006), and openness to experience (Andreassen et al. 2010; Aziz and Tronzo 2011) and negatively associated with neuroticism (Andreassen et al. 2010; Aziz and Tronzo 2011). While conscientiousness (Andreassen et al. 2010; Burke et al. 2006;

Aziz and Tronzo 2011) and neuroticism (Andreassen et al. 2010; Burke et al. 2006) were positively related to work drive, agreeableness was negatively associated with work drive (Andreassen et al. 2010), and openness to experience had contradictory associations with work drive (Burke et al. 2006; Aziz and Tronzo 2011).

The somewhat contradictory personality characteristics associated with the different facets of work addiction lend support to the notion subtypes of "workaholics." In this model, "enthusiastic workaholics" are highly involved with work, driven by internal pressure to work, and find great pleasure in doing so. Whereas "non-enthusiastic workaholics" are also highly involved in work-related activities and driven to work but seem not to derive enjoyment from doing so (Alvarez-Moya et al. 2007).

In the small domain of excessive exercise, researchers have found higher levels of harm avoidance and persistence and lower self-directness and less mature character among those who exercise excessively (Grandi et al. 2011). Among American university students, Hausenblas and Giacobbi (2004) found extraversion, neuroticism, and low agreeableness to predict exercise dependence symptoms. They reasoned that individuals with high neuroticism could be using exercise as a coping strategy for their stress or using exercise to address excessive worry or concern over their appearance/health. They also suggest that upbeat, energetic (extraverted) individuals may be drawn to exercise, and individuals who are low in agreeableness tend to be egocentric, skeptical of others' intentions, and competitive, with excessive exercising satisfying a competitive nature.

Few researchers have examined personality traits common to or differentiating between multiple addictive behaviors. In a Spanish study, researchers compared binge-eating disorders and pathological gambling with controls (Claes et al. 2012). They found that both eating-disordered individuals and pathological gamblers showed significantly higher scores on harm avoidance and lower self-directedness compared with control subjects. In addition, compared to control subjects, gamblers were characterized more by novelty seeking and persistence. Also in Spain, Alvarez-Moya and colleagues (2007) examined the personality risk factors in bulimia nervosa and pathological gambling and found high novelty seeking to be specifically associated with a diagnosis of problem gambling and low self-directedness to be associated with both bulimia nervosa and gambling. In addition, women with both bulimia nervosa and pathological gambling displayed higher harm avoidance and cooperativeness than control women, whereas men with problem gambling reported higher reward dependence and persistence than control men, highlighting potential differences between sexes.

Two studies examined compulsive buying and eating disorders. Davenport et al. (2012) found reward sensitivity and cognitive anxiety to be positively related to excessive eating and compulsive buying. Impulsivity was positively related to compulsive buying, whereas somatic anxiety and social desirability were negatively related. Claes and colleagues (2011) found compulsive buying among Belgian and German individuals to be positively related to BAS reactivity (fun seeking, reward responsiveness, impulsivity) and low effortful control,

whereas eating disorder symptoms were found to be related to high BIS reactivity (especially drive for thinness) and low effortful control. They concluded that compulsive buying is more impulsivity driven, whereas eating disorder symptoms (especially drive for thinness) are more anxiety related.

Finally, Walther et al. (2012) conducted a large German study examining personality factors related to substance use, gambling, and computer gaming. High impulsivity was the only personality characteristic associated with all addictive behaviors. Depression and extraversion were specific to substance users. Four personality characteristics were specifically associated with problematic computer gaming: irritability/aggression, social anxiety, attention deficit hyperactivity disorder (ADHD), and low self-esteem. Problematic computer gamers and gamblers did not match in any personality characteristics apart from high impulsivity. The authors argued that problematic gamblers seem to be more similar to substance users than problematic computer gamers.

91.2.4 Summary and Integration

A syndrome model of addiction (Shaffer et al. 2004) espouses multiple interacting biological, psychological, and experiential elements acting to initiate and sustain the syndrome. The psychological factors (i.e., impairment of control, craving, motives and expectancies, and personality) that we have discussed in this chapter comprise the shared components of the syndrome model. These psychological factors influence the expression of and fuel the maintenance of the addiction.

For example, experience of cravings and urges involve emotional experiences (e.g., desire, irritability, anxiety), cognitive effects (e.g., intrusive thoughts), physiological experiences (e.g., heart rate, respiration, salivation), and overt behaviors (e.g., seeking alcohol) (Rosenberg 2009). These response domains may be influenced by particular personality characteristics, and particular personality characteristics may influence how an individual responds to urges and cravings. Similarly, propensities towards particular motives may be associated with particular personality profiles. One's motive for engaging in behavior and expectancy of the outcome will determine whether or not the individual decides to engage in the behavior. He or she may engage in online gaming from a social motive, because of a tendency towards introversion and wanting to connect with others. Similarly, an individual may engage in behavior to cope (coping motive) with negative affect, which may be associated with a tendency towards neuroticism.

Neuroticism and impulsivity seem to be particularly relevant in addictive behaviors. The tendency to excessively engage in behavior as a form of escapism appears to be important and is in line with the notion that control over an impulse is often sacrificed in times of emotional distress (Tice et al. 2001). When individuals feel unpleasant emotions, they generally seek symptom relief, a desire perceived to be urgent, which undermines impulse control. This pattern and coping motive has been found in excessive behaviors such as problem gambling (Reid et al. 2011).

The excessive use of behaviors as a form of escapism or as a means to modulate affect might be indicative of a particular subtype of addictive behavior (Alvarez-Moya et al. 2010; Mueller et al. 2010; Vachon and Bagby 2009). Different personality characteristics may provide different motives for engaging in the same behavior. For example, an individual high on neuroticism may engage in gambling as a means to regulate emotional distress, whereas another individual (high in extroversion, sensation seeking, and novelty seeking) may gamble for thrill-seeking purposes (Vachon and Bagby 2009).

In addition to motives or precursors to engaging in a particular behavior, an individual's personality traits may lead to an individual's preference of one type of excessive behavior over another. For example, individuals high on extraversion may be more likely to engage in excessive work (Andreassen et al. 2010; Burke et al. 2006) or exercise (Hausenblas and Giacobbi 2004), whereas individuals low in extraversion may be more likely to excessively engage in online gaming (Charlton and Danforth 2010; Peters and Malesky 2008).

A syndrome model of addiction can be used to explain inconsistencies across behaviors. For example, personality characteristics (i.e., agreeableness and conscientiousness) not typical of some behavioral addictions (i.e., gambling) have been found to be associated with others, for example, facets of work addiction (Andreassen et al. 2010; Aziz and Tronzo 2011). Acknowledging the importance of motives and expectancies may help explain the personality profiles of individuals who engage in work excessively. Van den Broeck and colleagues (2011) divided controlled motivation for work engagement (working for external and internal rewards and avoiding punishments) from autonomous motivation (working for personal importance of an activity and interest). This division seems to fit with Andreassen and colleagues' notion of the "enthusiastic workaholic," who is highly involved with work, driven by internal pressure to work, and finds great pleasure in doing so, and the "non-enthusiastic workaholic," who does not to derive enjoyment from work (Andreassen et al. 2007).

What remains unknown is whether work addiction is qualitatively different (based on common personality characteristics) from other behavioral addictions or whether these excessive behaviors compose a heterogeneous group. Further research is required to examine the psychological components across behavioral addictions, particularly non-gambling behaviors. Examination of these constructs across and between the behaviors would clarify the homogeneity or heterogeneity of the group. Longitudinal research on personality is also required, allowing for measurement of enduring, "trait-like" personality risk factors for addictive behavior (Slutske et al. 2005).

91.2.5 Implications for Treatment

Personality traits often interact with other psychological factors and situational variables to produce emotional and cognitive states, which then result in certain types of

behavior. Particular personality characteristics may lead to interpersonal problems encouraging engagement in particular behaviors, and engagement of behaviors excessively may affect interpersonal difficulties. The implication of this dynamic interaction between personality characteristics, emotional and cognitive states, interpersonal problems, and excessive behaviors suggests that a model of treatment that targets or addresses all of these domains might be particularly effective.

The syndrome model of addiction highlights both shared and unique components of the syndrome and correspondingly, the treatment. The shared components aspect of the syndrome model suggests that behavioral addictions ought to be treated in the same way as substance addictions. There has been movement towards a transdiagnostic approach to treatment across mood and anxiety disorders (e.g., Ellard et al. 2010); perhaps a similar approach may be warranted for behavioral addictions. Ellard and colleagues established support for a dimensional conceptualization of psychopathology, targeting core affective factors of mood and anxiety disorders rather than diagnosis-specific symptoms. This transdiagnostic model aims to "address the dynamic and interacting nature of these disorders, or the true holistic experience" of the individuals (2010, p. 99). Furthermore, since behavioral and substance addictions have a shared sequelae, such as depression or anxiety, the syndrome model suggests that a concurrent disorder treatment approach is ideal that not only targets the "substance" or "behavior" but the sequelae as well.

Additionally, the unique components aspect suggests that there are particular idiosyncrasies that are specific to the addictions, which calls for differential or tailored treatment for each addictive behavior, depending on the psychological characteristics of the particular client. A "one size fits all" approach may not be appropriate. For example, clients excessively engaging in work may differ from those who engage in gambling. Thus, addressing agreeableness via communication skills training might not be an issue for workaholism (for those who score high on agreeableness), whereas it might be beneficial for gambling where it is negatively correlated.

The importance and dynamic nature of psychological factors in addictive behaviors suggests that treatment ought to target one or more of these psychological factors, depending on what the tailored case formulations suggest are most saliently sustaining the addiction or are most amenable to treatment. For example, cognitive-behavior therapy or motivational interviewing may be useful for targeting emotional and cognitive states, motives and expectancies, beliefs regarding impairment of control and craving, beliefs about the stability of personality, deception/denial, and counterconditioning to new activities. Interpersonal therapy and systems and family therapy might be beneficial for social and interpersonal aspects of the addiction. Pharmacological treatment may be beneficial in alleviating cravings and withdrawal, and relapse prevention and twelve-step programs may address the longitudinal nature of addiction. Finally, brief therapy or self-help treatments may be incorporated for a stepwise-care approach, recognizing the dimensional and dynamic nature of addiction severity. Just as the syndrome model of addiction is multifactorial, treatment ought to be multifactorial as well, suggesting that multi- and interdisciplinary teams might be a particularly suited and effective model of care. Future treatment research is warranted at many levels of analysis:

from dismantling studies that evaluate particular techniques within treatments, practice-based or process studies to examine the treatment program, and studies that evaluate an entire multi- or interdisciplinary program that can provide pharmacotherapy, psychosocial therapy, family therapy, and long-term care.

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Abstract

This chapter deals with the new developments in the treatment of disordered gambling, as well as with the challenges for further research. Abstinence versus moderated gambling as therapeutic goals is an issue that raises many concerns and that needs to be addressed. Current psychological treatment for disordered gambling involves a number of different options, including inpatient treatments, individual and group cognitive-behavioral options, Gamblers Anonymous, and pharmacotherapy, as well as an intervention in relapse prevention. Most of the treatment is delivered on an outpatient basis. Cognitive-behavioral therapy and motivational enhancement therapy may have a success rate ranging from 50 % to 80 % of treated patients in a long-term follow-up. Psychopharmacological therapy may have incremental benefit when patients have comorbid depression or high impulsivity. A relevant issue relates to treatment intensity and the emergence of a plethora of so-called brief interventions. Responsible gambling may be a therapeutic option for young gamblers or people without a severe

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dependence. Further information is required about treatment for online gambling addictions and for dealing with specific populations (e.g., women and young people). Unanswered questions for relapse prevention and future research in this field are commented upon.

92.1 Introduction

Gambling disorder (GD) is a relatively common and often disabling psychiatric condition characterized by intrusive urges to engage in deleterious gambling behavior in terms of time invested and money wagered, which results in significantly negative effects on gamblers daily lives and on quality of life.

Pathological gamblers often suffer from comorbid disorders, such as a mood disorder, bipolar disorder, generalized anxiety disorder, posttraumatic stress disorder, and substance addictions or personality disorders, such as borderline and antisocial personality disorder (Lorains et al. 2011).

In the DSM-IV pathological gambling was classified as part of "Impulse-Control Disorders Not Elsewhere Classified," which also included disorders like kleptomania, pyromania, and trichotillomania. In the new edition (DSM-5), pathological gambling, now renamed "gambling disorder," joins substance-related addictions in a group called "Addiction and Related Disorders." This reclassification of GD alongside other addictive behaviors is more appropriate. Classifying gambling disorder separately from other addictions drives an artificial wedge between substance addictions and behavioral addictions, even though there are many commonalities between them and they are treated using similar methods. GD is the only behavioral addiction in this category because it is the only disorder with enough existing data to progress with classification as an addiction (el-Guebaly et al. 2012). Further research is needed to consider other behavioral addictions, such as Internet addiction.

Another change is that, where in the DSM-IV there were ten behaviors listed reflecting different aspects of pathological gambling, in the DSM-5 there are only nine. Whether or not a gambler has committed an illegal act (like theft or fraud) to finance gambling is no longer considered a sign of GD. This behavior was, in fact, the least frequently found symptom on the DSM-IV. Illegal acts symptom is most helpful only for identifying those with the highest levels of gambling problem severity. In addition, DSM-5 reduces the number of criteria required for a diagnosis of GD from five to four.

DSM-5 criteria for gambling disorder focus on preoccupation with gambling, need to gamble increasing amounts of money, and repeated unsuccessful efforts to control gambling. From a clinical perspective, two elements are the most representative of GD: continuous or obsessional chasing of losses and family, job, and social disruption by gambling.

The prevalence of GD varies considerably across different studies. Anyway about 0.8–1.5 % of the adult population can be classified as probable pathological gamblers, while the prevalence of problem gambling is 2.5 %. In particular, substance abusers and patients seeking treatment for medical and psychological

disorders (e.g., anxiety and mood disorders) tend to have high rates of gambling problems. However, since the occurrence of PG varies from country to country and the measures for calculating the prevalence are not always the same, current estimates of the prevalence of GD must be treated with a degree of caution (Kessler et al. 2008).

Men are more likely to be gamblers than women and also more likely to develop gambling-related problems than them. However, there is evidence that gambling problems have increased among women in recent years. In addition, GD is associated with poorer measures of mental health in women compared to men. Women are more likely than men to gamble in order to relieve feelings of depression and anxiety and to escape dysphoria. Whereas men frequently begin gambling early in life, report slow emergence of problems, and seek help well after developing problems; women start gambling later in life, then rapidly develop dependence, and seek help more quickly (Echeburúa et al. 2011a).

92.2 Main Interventions for Gambling Disorder

92.2.1 Psychological Treatment

The interventions for GD that have been developed and reported in the literature are quite similar to methods of treating other addictions and include approaches that are psychoanalytic, behavioral, cognitive, pharmacological, addiction based and multimodal, and self-help. Often these approaches are combined to varying degrees in most treatment programs or counseling settings. Although gambling treatment dates several decades, few empirically supported treatments for GD have been developed.

92.2.1.1 Treatment Goals for Gambling Disorder

Abstinence versus moderated gambling is an issue that raises many concerns and that needs to be addressed. Like in the case of chemical addictions, the gold standard for disordered gamblers recovery is total abstinence. Abstinence is closely associated with recovery of pathological gamblers (Echeburúa et al. 2000).

However, complete abstinence from gambling may not be necessary for successful treatment in problem gamblers who have behavioral problems and negative consequences of gambling, but they are not still dependent on gambling. In these cases evidence supports strategies aimed at reducing harmful negative consequences incurred through involvement in risky behaviors. Controlled gambling can be defined as gambling in the absence of the subjective sense of impaired control and adverse financial consequences, based on self-rating and confirmation from a partner or significant other. Strict abstinence goals may discourage problem gamblers from seeking treatment.

Irrespective of the need of going on with clinical trials comparing therapeutic modalities with varying treatment goals, both goals are necessary for different kinds of patients. While abstinence-focused treatments are the best option for strictly

pathological gamblers, moderated gambling in a harm reduction approach may be interesting for problem gamblers or for a primary prevention approach. Therefore these goals are complementary strategies.

92.2.1.2 Effective Treatments for Gambling Disorder

Current treatment for GD involves a number of different options, including inpatient treatments, intensive outpatient, individual and group cognitive-behavioral options (CBT), and pharmacotherapy. Most of the treatment is delivered on an outpatient basis. Inpatient care is generally limited to patients with severe acute crises, treatment failures, and severe comorbid disorders, particularly depression and attempted suicide.

Behavioral Therapies

Behavioral approach considers gambling behavior as having three components: antecedents (financial pressure, gambling cues, positive or negative emotions, interpersonal factors, urges to gamble), overt or covert behavior itself (money spent in gambling, coping strategies to deal with anxiety or depression, thinking about gambling or about how to attain money), and consequences, both positive (autonomic arousal, opportunities to socialize, escape from personal problems, monetary gain) and negative (anxiety and depression, low self-esteem, work and relationship conflict, financial loss). Anyway gambling-based arousal is the central factor in the reinforcement process. Approach to gambling in regular gamblers is triggered by a wide range of environmental features: driving the car, leaving work, the sight of money in the wallet, and so on. Gambling is also highly reinforcing because of the variable pattern of reinforcement and the tension relief (Hodgins and Holub 2007).

Behavioral therapy considers pathological gambling a learned behavior and relies on techniques such as stimulus control, systematic exposure, and skill development (e.g., relaxation techniques and improving stress management and social skills) to reverse the learned behavior and the association between arousal and conditioned elicitors. Reduction in gambling is expected if patients can successfully develop and use alternative coping responses to deal with urges to gamble. Behavioral counseling, in which the gambler is given verbal reinforcement for desired outcome behaviors, and in vivo exposure, in which the gambler is exposed to gambling behaviors but is not allowed to gamble, are also mentioned in the literature (Hodgins and Holub 2007).

Stimulus control involves limiting access to money, not visiting venues that offer gambling and not spending time with people associated with heavy gambling. As treatment advances, the control of stimuli is gradually faded, except avoiding gambling friends and to signing up for the self-exclusion program. Recovering gamblers are also encouraged to take themselves off mailing lists from the casino, to meet with a financial planner, to cancel all credit cards, and to turn over control of money to another person. Self-exclusion from gaming venues can be an adjunct to treatment. Actually participants tend to comply with the commitment of abstinence and have more positive outcomes when they are also involved in complementary treatment or self-help groups (Nelson et al. 2010).

Table 92.1 Program of in vivo exposure in gambling disorder

Exposure	Characteristics
1st week of exposure	The co-therapist (a relative or a close friend) is together with the patient when he is practicing exposure to a slot machine
	The patient takes money only for his daily needs
2nd week of exposure	The co-therapist goes with the patient to the gambling site, but stays outside waiting for him when the patient is practicing exposure exercises
	The patient takes money only for his daily needs
3rd week of exposure	The co-therapist stays at home when the patient goes to the gambling site to practice exposure exercises. If the patient is in a jam, he can phone the co-therapist
	The patient takes money only for his daily needs
4th week of exposure	The co-therapist no longer takes part in the exposure task
	The patient takes money only for his daily needs

Exposure with response prevention is focused on making patients experience the desire to gamble and teach them how to resist it in a gradually more self-controlled way. The aim of systematic exposure to cues and situations of risk is to make the cues lose their power to induce urges and gambling behavior. If responses are prevented or controlled, the stimulus-response relationship will weaken. In addition patients are taught alternative strategies to cope with their increased anxiety. Exposure tasks take place 6 days a week for a minimal time of 15–20 min. Patients cannot drink alcohol or other drugs during the exposure tasks. Only stimuli relevant to the individual should be included if generalization is to occur in the natural environment. The characteristics of the application of this technique are shown in Table 92.1. This type of therapy is designed to deal with cravings and urges for gambling by increasing confidence in the ability to impose self-control over gambling.

McConaghy et al. (1991) randomly allocated 120 participants to aversion treatment, imaginal desensitization, imaginal relaxation, or in vivo exposure. Patients assigned to imaginal desensitization reported better outcomes at 1 month and up to 9 years later. In a further investigation of this sample, the abstainers and controlled gamblers showed a significant reduction in arousal levels, anxiety, and depression during the follow-up period compared with those who could not control their gambling (Blaszczynski et al. 1991).

Another behavioral controlled investigation with a wait list control group was done by Echeburúa et al. (1996). They compared the effectiveness of cognitive and behavioral techniques in a Spanish sample of 64 men and women who met DSM-III-R criteria for pathological gambling. Participants were randomly assigned to one of four treatments: individual stimulus control and in vivo exposure with response prevention, group cognitive restructuring, a combination of the first two, and a waiting-list control group. At 12-month follow-up, the most favorable outcome was associated with the first two groups, which reported therapeutic success rate (abstinence or one or two gambling episodes in which the amount

gambled did not exceed the amount gambled in the week prior to treatment) of 69 % and 37 %, respectively. The behavioral therapy was found to be more effective than the group cognitive restructuring in terms of reducing gambling frequency.

Grant et al. (2009) compared a six-session CBT program, combining imaginal cue-exposure plus the negative mood induction (focused on the negative consequences of gambling while the urge is active) with GA. The 64 % of participants assigned to behavioral program maintained abstinent at 1-month follow-up as opposed to only 17 % of patients assigned to GA.

In sum, according to the meta-analysis of Pallesen et al. (2005), interventions involving developing relaxation skills, exposure to gambling cues, and direct behavioral action are effective in improving gambling urges, time and money spent, and abstinence. In addition, behavioral change is related to cognitive change after treatment.

Cognitive-Behavioral Therapies

Excessive gambling can be driven by distorted and maladaptive cognitions, such as illusion of control, superstitious thinking, or misperception of probability. Two major beliefs (gambling outcomes can be correctly predicted and controlled) appear to describe the problem gamblers' irrational cognition. Disordered gamblers believe they have the ability to control random or chance events by relying on superstitious behavior or methods. This illusion of control is stronger as gamblers become more familiar with a game. Thus they can believe that a big win is imminent and persists despite mounting losses, with an unrealistic hope that they will recover their losses if they persevere with the gambling (the gambler's fallacy) (Ladouceur and Walker 1998).

Cognitive therapy aims to help patients challenge and overcome irrational thoughts that are believed to initiate and maintain the undesirable behavior. Patients are taught to be aware of the link among thoughts, behavior, and emotion. Many patients do not understand the concepts of probability and randomness, believing that they can exert some control over whether they win or lose. Treatment typically involves teaching patients strategies to correct their erroneous thinking by providing corrective information through education, logical discussion, or behavioral experimentation. Thus the therapist will ask the gamblers to describe what they are saying to themselves when gambling. If the erroneous perceptions and understanding of randomness in the gambler can be corrected, then the motivation to gamble should decrease dramatically. Cognitive therapy also aids gamblers in coping with urges to gamble, managing negative emotions and training in problem solving techniques (Ladouceur and Walker 1998).

The more recent randomized clinical trials have focused on combined cognitive and behavioral approaches (cognitive correction, problem solving training, and social skills training). In two different trials Ladouceur et al. (2001, 2003) compared a 12-month follow-up individual and a 24-month follow-up group CBT (ten weekly sessions), respectively, with a wait-list control group. In the second trial a relapse prevention component was also included. People receiving treatment met fewer DSM criteria for pathological gambling, and treatment gains were

maintained over the follow-up period. However, dropout rates were high (47 % in the first trial and 26 % in the second one).

An individual eight-session manualized form of CBT has also been compared (either delivered by a professional counselor or completed alone by the patient in a self-help workbook) with a group referred to GA. Although participants in all groups reduced gambling, CBT in both conditions was better than GA in terms of days gambled and number of gambling criteria met. In the GA group attendance at meetings was positively associated with abstinence from gambling (Petry et al. 2006).

In the Jiménez-Murcia et al. study (2012), exposure and response prevention do not improve the results of a group CBT for male gamblers due to its increasing effect on the dropout rates. However, in other studies with different results, exposure and response prevention are used together with stimulus control in a behavioral management program and in an individual format (e.g., Echeburúa et al. 1996, 2000, 2011b).

In sum, both individual and group CBT appear effective for reducing gambling. Individual CBT may be enhanced if patients receive compliance-improving interventions, such as a reinforcement of self-efficacy, reminder phone calls, assessment feedback, and a weekly decisional balance exercise to complete. Group CBT may be enhanced if individuals have interactive written exercises. In this way that mapping may serve to individualize the group treatment, leading to greater effect (Melville et al. 2004).

However, the cognitive therapy studies have not yet determined the optimal number of sessions needed to reduce gambling symptoms and maintain improvement (Grant and Odlaug 2012).

Motivational Enhancement Therapy

Another approach adopted to help problem gamblers focuses on the use of short-term brief motivational enhancement therapy and telephone counseling, mailed self-help workbooks, and online resources. Brief treatment is defined as that using less professional resources or time (four or fewer sessions and sometimes one single session) than usual face-to-face interventions (typically, six to twelve sessions of therapist contact). This therapeutic modality may be an important innovation to helping people with gambling problems who fail or refuse to seek treatment in traditional therapeutic settings and may enhance patients' sense of control over their own recovery (Hodgins and Holub 2007).

Motivational interviewing (MI) focuses on patient's intrinsic motivation for change and on patient's strengths to enhance self-efficacy. Motivational interviewing strategies act in some way to resolve ambivalence and promote greater commitment to change.

This approach has proven to be effective, at least with those with less severe gambling problems (Hodgins et al. 2001). In the latter study, at a 24-month follow-up, 77 % of the entire sample was rated as improved, but gamblers receiving the workbook and a telephone motivational support reported less frequent gambling and lower severity scores than workbook-only group. In other studies of the same

group (Diskin and Hodgins 2009; Hodgins et al. 2009), patients who received the motivational interviewing plus workbook gambled less and spent less money than workbook-only group.

A combined motivational interviewing and CBT program applied in group or individual format, or even adapted to a web-based format (Carlbring and Smit 2008), can improve GD behaviors, as well as gambling correlates. Moreover the addition of motivational interviewing to CBT can reduce treatment attrition and improve outcomes (Wulfert et al. 2006).

However, these motivational approaches, which are more attractive to gamblers and may result in an increase of treatment seekers, cannot be so effective with severe pathological gamblers or patients with comorbid pathology. More research is needed to determine the efficacy of these programs when compared to more established CBT.

Gamblers Anonymous

Modeled after the traditions and spiritual principles of Alcoholic Anonymous, Gamblers Anonymous (GA) is the primary self-help group and uses an abstinence-based treatment program. DG is conceptualized as an illness which can be arrested but never cured, so people affected by this problem have a permanent predisposition for losing control over their gambling.

The therapeutic rationale for GA is that the 12 steps to recovery will lead gamblers to attain abstinence. The group format is intended to provide a sense of common purpose and understanding, emotional and spiritual support, and hope. Anonymity allows for members to feel safe in sharing openly with other members (Hodgins and Holub 2007).

The efficacy of GA has not been demonstrated in controlled studies. Relapse rates tend to be quite high. Stewart and Brown (1988) found that total abstinence was reported by only 7.5 % of members surveyed 1 year after their first attendance and by 7.3 % at 2 years. Attrition rate is also high. People attending GA have better gambling outcomes than those who do not, even though they are engaged in professional treatment concurrently (Petry et al. 2006).

The therapeutic effectiveness of Gamblers Anonymous has also been explored with respect to participation by the gambler's partner. There is a trend for higher abstinence rates for gamblers whose partners are present at meetings compared with gamblers whose partners do not attend.

There is a particular need for studies of the role of GA in recovery and treatment outcomes. A recent study found that there were not any differences on key gambling variables (e.g., frequency, abstinence rates, money wagered) at 12 months between a program of CBT and 12-step therapy (Toneatto and Dragonetti 2008). If there is a high dropout rate from Gamblers Anonymous, as the literature suggests, then it is important to investigate its causes and strategies for reducing it.

In sum, GA may be increasing in popularity, but whether participating in meetings makes a significant and lasting impact is still not well known.

92.2.1.3 Relapse Prevention

A challenge in the treatment of pathological gambling is preventing relapse. Many personal and environmental factors interact to influence the risk of relapse for any individual trying to recover from an addiction. Relapse prevention is focused on training patients to identify high-risk situations for relapse, such as social pressure, negative emotional states (e.g., anxiety, depression, and anger), and interpersonal conflicts, and providing them adequate strategies for coping with problematic situations. Pathological gamblers are deficient in the number of coping skills they have available and in their ability to flexibly choose the skill most appropriate to the stressful, or potentially relapse-triggering, situations they face. Relapse prevention techniques increase the likelihood of engaging in adaptive coping behaviors.

Successful recovery also involves the development of new skills (e.g., cognitive reframing) and lifestyle patterns that promote positive patterns of behavior. The integration of these behaviors into day-to-day activities is the essence of relapse prevention.

The problem solving approach is oriented to increasing the gambler's abilities to cope with urges or cravings and to deal with anxiety, depression, or personal crises for which the gambling is an escape. For example, substance abusers with a gambling problem utilize significantly more avoidance and impulsive coping styles.

Echeburúa et al. (2000) evaluated the efficacy of providing relapse prevention strategies as a follow-up to behavioral treatment focused on total abstinence from gambling. Sixty-nine pathological gamblers received behavioral treatment (stimulus control and exposure with response prevention), followed by random assignment into one of the three conditions: individual relapse prevention, group relapse prevention, or no treatment control group. The results related to the 12-month follow-up relapse showed a success rate higher in both individual (83 %) and group (78 %) relapse prevention than in the control group (52 %). There were no differences between both experimental modalities. These results raise the need of relapse prevention programs in the treatment of pathological gambling. This study reported a dropout rate of 14.5 %. On the other hand, most relapses were observed in the first 3 months after treatment. The main triggers of relapse were inadequate money management, negative emotional states, alcohol abuse, craving, and social pressure (Echeburúa et al. 2001).

92.2.2 Pharmacotherapy

Pharmacotherapy is a relatively new approach to the treatment of GD and may be effective for reducing gambling urges and behavior. A variety of medications have been examined with varying results. Actually there are no approved medications for the treatment of pathological gambling (Grant et al. 2012).

Neurobiological studies suggest the involvement of serotonin, norepinephrine, and dopamine in GD because these transmitters are strongly associated with reward pathways. The norepinephrine system has been associated with arousal and novelty seeking, dopamine with reward and motivation, and serotonin with impulsivity and compulsivity (Hollander et al. 2005).

The medications target one or more of these neurotransmitter systems. The current pharmacological strategies for treating GD suggest the use of serotonin reuptake inhibitors (SSRI), mood stabilizers, atypical antipsychotics, and opioid antagonists.

SSRI antidepressants can reduce urges to gamble or prevent from compulsive behaviors. The rationale for this medication is the phenomenological association between GD and compulsivity. These medications are also helpful if anxiety disorders are associated to GD (Potenza 2012).

Opioid antagonists (naltrexone) can block feelings of euphoria related to gambling behavior and result in reductions of gambling urges and thoughts and in improvement in psychosocial functioning. The rationale for this medication is the similar neurological pathways for GD and substance addictions and the commonalities between clinical symptoms of both disorders. This class of medication, dosed at 50 mg/day, should be considered a first-line treatment for GD (Grant et al. 2012). Naltrexone may be particularly helpful for those with strong gambling urges at treatment onset and/or a family history of alcoholism (Potenza 2012).

In turn, mood stabilizers, such as lithium or topiramate, can reduce the use of gambling to regulate negative mood (most of all, if bipolar tendencies are present), but some recent controlled trials have failed to show any significant treatment effect for topiramate on the primary or secondary outcome measures.

Another avenue of approach is the use of medication to treat comorbid conditions. In practice, this is probably the most frequently cited reason for putting gamblers on medication. Comorbid disorders for which medications are commonly prescribed include depression, bipolar disorder, and attention-deficit hyperactivity disorder.

In sum, certain medications may be beneficial in treating this disorder. Pharmacotherapy research needs to be expanded to determine if this approach has an important role in the treatment of pathological gamblers and plays an adjunctive role to psychological treatments. We still do not know if medications provide therapeutic effect by ameliorating the pathological gambler's cravings, ruminations, or negative feelings. Heterogeneity of GD treatment samples may also complicate identification of effective treatments. In addition, some studies have reported high placebo response rates (Potenza 2012) and high rates of study dropout (30–50 %) (Petry 2005).

92.2.3 Issues in Treatment

Only a small proportion of the individuals who are suffering from GD (about 6 %) seek formal treatment. The satisfactions provided by their addiction, a desire to

handle the problem by themselves, and shame have been identified as contributing factors to resistance to treatment. Motivation becomes adequate when people identify gambling as a destructive agent in their life. Natural recovery from problem gambling can occur in about 35 %, but most disordered gamblers report a chronic course, with symptom severity fluctuating over time (Grant and Odlaug 2012).

Therapists have been confronted with the problem of treatment compliance. For pathological gamblers, compliance is an issue because they are often ambivalent about giving up their gambling or altering long-standing patterns of coping, no matter how ineffective. Some people do not seek treatment, some drop out after one or two sessions, and some can decide to terminate treatment after a few weeks thinking that their problem has been solved. It is a challenge to identify the characteristics and the reasons of individuals who refuse treatment, drop out, or simply do not show up for the first session. There are no obvious solutions to these matters, but motivational enhancement therapy, behavior contracts, and flexible treatment goals might improve treatment compliance.

Despite the growing trend toward harm reduction strategies and controlled behavior approaches for addiction problems, most gambling treatment programs, like those that treat substance abuse, favor abstinence. Some programs, however, particularly those dealing with problem gamblers in their early stages, aim at reducing and controlling rather than stopping gambling. Anyway clinical trials comparing treatments with varying treatment goals are necessary (Ladouceur et al. 2009).

A relevant issue relates to treatment intensity and the emergence of a plethora of so-called brief interventions. A distinction should be drawn between minimal intervention or advice in a primary care setting and brief intervention within a specialist context (one to three sessions). It is difficult to know if there are remarkable differences between brief and extended interventions for pathological gamblers. For instance, there are important differences between treatment-seeking populations as distinct from those that are selected as a result of opportunistic screenings. Anyway it is relevant to investigate the active ingredients of brief interventions which seem to be, at least, relatively successful (Grant and Odlaug 2012).

Interventions should be tailored to the needs of the patients. Substantial progress has been made in understanding the treatment of this disorder, but there is not yet research basis for matching patients to treatments according to different characteristics (e.g., subtypes of gamblers, different type of gambling, or gender of gamblers). That is, individuals with gambling problems cannot be treated as a homogeneous group, but refinement in matching treatment strategies with gambler typologies must await completion of controlled treatment studies.

Advances in family therapy for treating substance abuse problems have been adapted for gambling disorders, such as a self-help workbook of the Community Reinforcement and Family Therapy (CRAFT) model (focused on the training of family members to use behavioral principles to reinforce non-gambling behaviors) (Hodgins et al. 2007) or a coping skills training program for those with a pathological-gambling partner (Rychtarik and McGillicuddy 2006). Further research is warranted to improve the design and targeting of these approaches.

92.2.4 Internet Gambling

Internet gambling can be defined as any type of wagering that takes place by using the Internet. Common forms of online gambling are online poker, online casino, sports betting, and online bingo; though, there are some other ways to gamble using the Internet that hold strong potential for additional growth, e.g., gambling by mobile devices and gambling on the Internet games (Laplante and Braverman 2010).

Men are more likely to gamble using the Internet than women. Emotional states, maladaptive cognitions, and life events can serve as triggers for Internet abuse. The pervasiveness of Internet gambling sites on the web makes it an especially risky form of gambling. One of the most attractive features of Internet gambling is its convenience (e.g., playing comfortably at home and at a convenient time is reported to be the most important reason for playing online poker). The anonymity of Internet gambling presents an opportunity for the development of gambling-related problems. For example, because of anonymity, people may gamble under the influence of alcohol or drugs, be underage, or even gamble from the school or workplace. Solitary gambling, like Internet gambling, where people can gamble at their own pace with no outsiders interrupting or any other distractions, is also a risky factor. Computers and the Internet create isolation and a sense of fantasy. In summary, a cursory consideration of numerous risk areas logically suggests that the Internet might increase the speed of the negative effects of gambling or exacerbate gambling-related problems (Griffiths and Barnes 2008).

Minors might gain access to a credit card and gamble with other people's money. This raises concerns that children and adolescents' participation basically is unrestricted. In addition to being illegal, such an occurrence would be problematic because early exposure to gambling is linked with the development and persistence of gambling-related problems (Derevensky and Gupta 2007).

Appropriate treatment for online gambling addiction is still being researched. Treatments that are effective for gambling addiction work well for online gambling addiction. It is important to consider the individual needs when devising a treatment plan to tackle an online gambling addiction. Every person is different and could be addicted for different reasons.

Stimulus control involves for the Internet gambling addicts to engage in opposite activities, use of timers to end online sessions, set time limits, prioritize tasks, and record Internet usage to abstain from Internet abuse.

Group therapy is commonly suggested as a treatment option as well. If patients are attending support groups such as GA, they can use that group to help cope with their online gambling addiction.

Online gambling addiction, gambling addiction, and Internet addiction, which are all closely related, can create problems outside of the individual. They can cause damage to one's finances, marriage, and even their entire family. In these cases, financial counseling, marriage counseling, and family therapy are all beneficial treatment options.

In conclusion, a combination of individual, family, and group therapy may be the best option, although individualization should be emphasized. Medication (e.g., SSRIs) may be needed to treat associated anxiety or depression. Anyway our understanding of Internet gambling is still quite limited. There is no evidence-based research for treatment options regarding this topic.

92.3 Concluding Remarks

Behavioral and cognitive-behavioral therapy appear to be the most successful treatment approaches in different formats (individual, group, and self directed), regardless of the type of gambling behavior practiced (Gooding and Tarrier 2009). However, it continues to be controversial which form of CBT is best and for whom and what is the optimal duration of therapy. Many behavioral interventions often include cognitive components, so it may be difficult to isolate the most potent agent of change. However, the presence of irrational beliefs and attitudes about gambling in pathological gamblers do not always justify to confront them with a cognitive approach. Interestingly, a behavioral approach, which is focused on short-term cessation of gambling behaviors, can also result in a decrease of erroneous beliefs of patients, without treating them specifically (Echeburúa et al. 2000).

Both individual and group CBT appear to be effective in the treatment of GD and its correlates. Group therapy is not only just cost-effective; it also enables gamblers to learn from and support each other. Individual therapy may be more suitable for those who can afford therapy and those who prefer discussing life events on a one-to-one basis (Oei et al. 2010).

Pharmacotherapy appears to have a role in the treatment of coexisting depression, rather than as a primary treatment for GD. However, research on the pharmacological treatment appears promising, particularly in the case of opioid antagonists. There is growing recognition that multiple treatment components should be considered given the patient's specific configuration of problems. Thus, patients with dysphoria should be evaluated for antidepressant medication; family therapy may be indicated in the presence of extreme family estrangement; and substance abuse counseling may be necessary for those whose addictive behavior also includes alcohol or other drug abuse. Inpatient programs for severe pathological gamblers, with comorbid disorders or attempted suicide (or suicidal ideation), continue to be in use, but more rigorous research on effectiveness is warranted because to date there are no randomized trials (Grant and Odlaug 2012).

Very few studies have examined the combination of drug and behavioral treatments. Similarly, despite their high rates, there have been very few studies on the treatment of GD in conjunction with comorbid disorders, such as depression and personality or drug- or alcohol-use disorders. Irrespective of the effectiveness of CBT for pathological gamblers with or without other mental disorders, treatment must be adapted to these different circumstances. Thus gamblers who have

comorbid schizophrenia may require more sessions of therapy (i.e., 20 sessions), and a treatment focused more on behavioral than on cognitive components (Echeburúa et al. 2011b).

As problem gambling significantly affects patients relationships with their families, interventions for gambling problems have also been directed at affected families. Family interventions are at an early stage of development and evaluation. It will be important to determine their efficacy and cost-effectiveness compared to treatment provided to the gambler alone (Hodgins and Holub 2007).

Virtual counseling (Internet or computerized therapy) is another treatment option. Presently there are only a few gambling specialty treatment programs, and one way to expand treatment services is to provide telephone and Internet counseling. Some pathological gamblers may be reluctant to enter individual or group therapy due to stigma, lack of resource availability, or denial. Numerous chat rooms have emerged for GA 12-step fellowship and are available anonymously 24 h a day.

Gambling studies should focus particularly on treatments that have manual-guided treatments. Poor specification of the therapeutic methods used hinders the replication of successful programs. Not only do therapist's manuals guide interventions but they also facilitate the clarification of the specific contribution of particular treatment components.

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The National Problem Gambling Clinic 93

Henrietta Bowden-Jones and Neil Smith

Contents

Abstract

The National **Problem Gambling** Clinic is the first and only **National Health Service** clinic (provider of free state medical treatment) designated to the treatment of **pathological gamblers** from all over the UK.

The current prevalence of problem gambling in Great Britain is 0.9 % according to the latest British Gambling Prevalence Survey (NatCen 2010). This showed a 50 % increase since the previous survey of 2007 reported a prevalence of 0.6 %.

Currently therefore, there are deemed to be at least half a million **pathological gamblers** in the country with as many more scoring on screening for at-risk behaviors in relation to gambling (Natcen 2010).

Our clinic was set up by Dr. Henrietta Bowden-Jones as a direct result of the public concerns at a time when the British government was planning to allow the construction of several more casinos and when advertising gambling products had become legal.

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N. el-Guebaly et al. (eds.), *Textbook of Addiction Treatment: International Perspectives*, DOI 10.1007/978-88-470-5322-9_74,

The idea behind the project was to provide patients with a gold standard, evidence-based time-limited service providing specialist treatment delivered by psychologists and psychiatrists.

We have now had over 3,000 referrals and own the largest problem gambling database in Europe, and the amount of information collected has allowed us to reach in-depth understanding of the clinical subtypes presenting.

93.1 Introduction

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93.2 The Clinic Activities

Our clinic was set up by Dr. Henrietta Bowden-Jones as a direct result of the public concerns at a time when the British government was planning to allow the construction of several more casinos and when advertising gambling products had become legal.

The idea behind the project was to provide patients with a gold standard, evidence-based time-limited service providing specialist treatment delivered by psychologists and psychiatrists.

We have now had over 3,000 referrals and own the largest problem gambling database in Europe, and the amount of information collected has allowed us to reach in-depth understanding of the clinical subtypes presenting.

The types of gambling that patients are involved in are also recorded.

The most frequent activities are sports betting and electronic roulette machines, called fixed odds betting terminals in the UK. Internet gambling is increasing and about a third of our patients are now doing this regularly, sometimes to the exclusion of land-based gambling following a migration of habit.

Personal and psychiatric histories are also collected in an attempt to link activity and experience to outcomes; this is particularly relevant when we look at early adverse events in childhood and their predisposing negative impact on future illness.

Our patients tend to be male and aged between 30 and 40 years old, and most will be in either full-time or part-time employment.

Many, 84 %, have committed illegal acts to fund their gambling at some point in their lives.

Twenty percent have lost their jobs due to gambling, and 50 % have lost significant relationships such as their marriage due to gambling.

Many of the patients we see are depressed or anxious at the time of assessment and about a third have lifelong comorbid presentations, at times with severe and enduring mental illnesses such as schizophrenia.

Our approach is to treat everyone apart from the acutely psychotic patients, but even then, we advise on the best antipsychotic and agree to delay treatment temporarily so we do not turn people away as our strength is in understanding the complexities of dual diagnosis presentations.

The yearly funding for the treatment of what are now over 700 referrals a year comes in several ways, but the main bulk of the money, about £330,000, is received from the Responsible Gambling Trust, a government charity set up to distribute voluntary donations from the gambling industry to avoid a compulsory levy based on earnings.

Other funds come from government working parties attended by the Director of the clinic, court reports written by forensic psychiatrists trained at the clinic in pathological gambling expertise, industry training days, some Employee Assistance work, and lecturing fees. Further funds come via the successful research grant applications that may free up the clinical time of some researchers to contribute in clinical time for the access to problem gamblers in research projects of which there are many.

Although cognitive behavioral therapy is deemed to be a highly effective way of treating problem gamblers, we do offer other interventions such as a Money Management assistance service which in the UK is funded by the banking world to assist people with mental health issues. This service provides a session of psychoeducation around managing finances but also individual help with setting up repayment plans.

Another integral part of the clinic is the assistance we offer to relatives and carers of problem gamblers. Often, it will be an elderly mother who has read about us in the newspapers and has referred her son for treatment. At other times, spouses of gamblers are brought into clinic once the patient begins therapy. The support we offer to carers is also manualized and linked to psychological outcomes to determine the usefulness of the intervention, but we are more relaxed about our data collection as we really do want to help the individuals feel more supported in their suffering.

93.2.1 Treatment

Pathological gamblers who attend our clinic are offered a 90-min face-to-face assessment with a clinician. This assessment covers current and previous gambling history including first gambling experiences and emotional links to the gambling, for example, some patients only spent time with their father in childhood when they

were gambling. This has important implications for the right treatment approach as we do offer some more psychodynamic treatment for some patients who need a more interpretative approach. A history of medical and psychiatric difficulties is also taken along with any history of parental gambling problems. A brief personal life history is also obtained. Clients also complete a comprehensive battery of questionnaires including gambling and mental health screens. All assessments are discussed in a weekly multidisciplinary team (MDT) meeting where decisions are made regarding treatment packages offered.

The basic treatment offered by the clinic is an eight-session cognitive behavioral therapy treatment developed from work conducted by Nancy Petry (2005; Petry et al. 2006). The treatment is manualized in the sense that there are a set number of sessions and each session topic is guided by a specific handout. Within this protocol, therapists are expected to deliver the treatment flexibly in order to best meet the client's individual needs. Homework is an essential component of this treatment, with each session topic having comprehensive handouts including homework tasks. Clients are informed that homework is essential to change. Topics covered include stimulus control, rewards, coping with cravings, increasing pleasant activities, trigger management, understanding lapses, coping with gambling thoughts, and managing lapses. The treatment includes a strong psychoeducational component where clients are socialized to an addiction model of problem gambling, drawing on research from scanning studies to highlight commonalities with drug and alcohol addiction. This serves to "normalize" the problem and reduce confusion and the degree of personal guilt and judgment that clients often present with.

The service is guided by the "pathways model" of problem gambling (Blaszczynski and Nower 2002). This seminal paper suggested that three levels of severity of difficulties can be observed in problem gamblers. These levels relate to different etiological factors for problem gambling and increasing levels of associated and comorbid difficulties, with each level requiring more intensive treatment. In the MDT, a decision is made as to whether the individual assessed is of a "lower," "moderate," or "higher" severity, based on criteria derived from the pathways model and from internal audits of client characteristics.

Patients who present at the "lower" end of the severity spectrum are offered a brief intervention. This comprises the provision of an 85-page self-help workbook, with four individual sessions with a therapist. The workbook contains all handouts from the eight-session CBT treatment, with guided self-help exercises included.

Clients assessed as being of "moderate" severity are invited to attend the eight-session manualized treatment delivered in a group format. These sessions are of 90 min length and up to 20 individuals are invited to each group. Sessions involve group feedback of progress and homework and delivery of session topic content and finish with reflections on the session and homework for the coming week. Groups are strongly encouraged by the service; gathering with other individuals has the effect of normalizing a problem that often presents in highly isolated individuals.

Clients assessed as being of "higher" severity will receive the eight-session group CBT program plus additional individual CBT sessions with a therapist.

Each of these types of additional intervention is designed to prevent relapse and provide a solution for the problem of the "revolving door" in addiction services where clients with more severe difficulties often represent multiple times. These sessions may be offered for three reasons: additional support for gambling problems, provision of support for related comorbidity, and cognitive formulation work. Additional support for gambling is offered if individuals have not achieved control over their gambling by the end of the eight-session program or the clinicians are concerned that abstinence may only be temporary. The provision of support for related comorbid difficulties focuses on obvious comorbid, and often premorbid, psychological difficulties such as anxiety or depression that may hinder ongoing recovery. In the case of more severe comorbid difficulties, care planning for referral onto specialist mental health services will take place. The cognitive formulation is an intervention that provides an understanding for the client as to why gambling has become problematic for them. It may also help with other difficulties in the client's life that hinder recovery. The cognitive formulation follows methods pioneered by Aaron Beck of establishing how childhood experiences may contribute to negative core beliefs and the development of subsequent dysfunctional rules and strategies in adult life. In clients with gambling problems, it is very common to observe adverse upbringings leading to the development of core beliefs of "failure" or "defectiveness." These can leave an individual vulnerable to addiction if exposed to gambling. Understanding these core beliefs and challenging them are often an essential part of treatment.

The core eight-session manualized CBT treatment may be delivered by individual therapists instead of in a group format under one of the following three conditions: language difficulties, risk issues to self or others, and low intellectual functioning. Individuals who are anxious about group working are encouraged to try out groups prior to opting for an individual CBT treatment.

We also offer a brief Motivational Enhancement Intervention for individuals who may be unsure as to whether they have a gambling problem. This comprises a four-session treatment with a therapist using motivational enhancement principles to guide discussions about the gambling behavior. If, as often happens, during these sessions the individual decides they do have a problem and wish to change, then the therapist delivers the manualized CBT treatment.

As not all individuals can be grouped together in the main CBT program due to different levels of cognitive functioning, special group programs for the following distinct populations have been established: a women's group for emotionally vulnerable women who present with significantly low mood and anxiety and a reticence to attend the predominantly male groups, a homeless persons group held either at the clinic or in a homeless hostel and funded by the homeless national services, and a mental health group. All follow a modified version of the core CBT program.

Following the completion of treatment, each individual has a discussion with their therapist as to whether they feel they have received a sufficient intervention to help them combat gambling difficulties. With the group program, this is delivered by telephone following the end of the eight group sessions.

If individuals are happy with the treatment they received, they are invited to attend the Aftercare Group. This is held once a month and patients who complete treatment can attend for as long as they wish. The Aftercare Group is an open-forum group; facilitators start by setting an agenda of topics that the attendees wish to discuss. These topics may involve positive or negative experiences of recovery. The conversations are then steered by the facilitators to cover the topics in the manualized treatment. The group serves as a reminder for individuals of techniques and strategies learned in the CBT sessions they attended. Members are invited to support each other within this group, but preferably by suggesting techniques from the manualized intervention.

93.2.2 Education and Prevention

Because the clinic is the only one, it has a significant role in British society that goes far beyond its remit to treat problem gamblers.

Here is a list of activities we believe a National Clinic needs to attend to as well as deliver high-quality treatment:

- Any time a newspaper article or other media program is planned, the clinic will be asked to contribute to it in light of its expertise and perspective.
- The aim for us is to remain as politically neutral as possible while still enforcing what we believe are fundamental societal needs to protect gamblers, such as adequate self-exclusion policies, the protection of children and young people from the proliferation of gambling products, the need for more stringent laws around advertising gambling activities, and ensuring enough attention is paid to the quality of treatment services at a national level when they fall outside the remit of the NHS.
- Peer-reviewing journals.
- Training the next generations of psychiatrists and psychologists.
- Maintaining links both nationally and internationally in the field writing articles on case studies and disseminating knowledge about problem gambling to professional groups (Bowden-Jones and Clark 2011).
- Lecturing to medical students and other mental health professionals on the topic of problem gambling.
- Teaching the general public about the issues via open lectures and invited talks.
- Facilitating the work of the neurobiological research group currently neuroimaging the gamblers.

All of the above need to be addressed and constantly updated if we are to continue leading the way in the UK.

Our hope is that in the future, the State will recognize the need to fund problem gambling treatment throughout the UK and include pathological gambling in the illnesses it recognizes. The need for smaller clinics set up to be linked up to our central "hub" is a cost-effective one that we will be working on for years to come.

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Internet Addiction

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Abstract

This paper investigates the concept of Internet addiction disorder (IAD). The phenomenon of excessive Internet use is increasingly becoming a public health issue. Increasing research evidence indicates common clinical, neurobiological, and neuroimaging findings between IAD and addictive disorders. Different clinical descriptions and research findings suggest however the existence of various types of Internet addictions (i.e., gaming, cyberpornography, etc.). The Internet could be then rather the facilitating vector of an addiction to a given behavior linked to specific stimuli and operant conditioning mechanisms.

As an attempt to increase understanding and knowledge related to IAD, a number of screening tools were studied. Various forms of excessive Internet use or IAD seem also associated with a number of coping strategies as well as personality characteristics and possible comorbid psychiatric disorders.

In spite of a number of clinical treatment programs dedicated to IAD, there are still limited publications on the efficacy of such treatments. The few existing ones mostly relate to interventions inspired by cognitive-behavioral therapy.

The determinants, the evolution of the possible IAD-related disorders, as well as the validation of adequate treatments are yet to be clearly established. Longitudinal studies using large and representative samples are required.

94.1 Introduction

Internet addiction disorder (IAD) is increasingly becoming an issue, especially in adolescents, the most studied subpopulation. Various deaths in cybercafés (Choi 2007) and videogame-related murders (Koh 2007) have been reported. Moreover, a significant number of adolescents are reportedly in need of treatment (on average ten million Chinese and 2.1 % of 6–19-year-old South Koreans) (Ahn 2007). This has led some countries (i.e., China and South Korea) to consider IAD as a serious public health issue (Block 2008). The European Union also funded a multisite prevalence study into adolescent problematic Internet use (PIU). The findings showed a prevalence rate of 4.4 %, with some variation between countries (Durkee et al. 2012).

IAD is an emerging concept that has not yet been refined. It refers indiscriminately to excessive Internet use and problematic Communication and Information New Technologies (CINT) use (e.g., cell phones). This concept is starting to generate debate within the scientific community. There is some reluctance to "pathologize" human behaviors. There is also a need to avoid qualifying every passionate or extensive engagement in pleasurable activities as a disorder (e.g., gambling, chatting, watching pornography, gaming). If a new medical concept (e.g., IAD) arises, the question is how to scientifically define the cutoff between nonproblematic, problematic, or pathological use.

The disorder was first described in 1998 by Kimberly Young (1996) as including numerous symptoms that are similar to the criteria for addictive disorders. These include (a) tolerance (i.e., the need to spend increasing amounts of time using the

Internet and withdrawal symptoms such as irritability and tension), (b) preoccupation, (c) inability to cut back, and (d) negative consequences for private, social, and professional life. Three separate categories have been identified: excessive video gaming, obsessive and compulsive sexual behaviors, and overuse of social networks (Block 2008).

Increasing research evidence indicates common clinical, neurobiological, and neuroimaging findings between IAD and substance use disorders (SUD). This body of evidence suggests that the addictive spectrum hypothesis is the most appropriate conceptualization of IAD. These findings have led to the consideration of IAD for inclusion in the forthcoming Diagnostic and Statistical Manual of Mental Disorders (DSM-V) (Block 2008). It was however not included in the DSM-V. More studies on IAD and on Internet gaming disorder (see chapter VI for more details) and other forms of Internet addictive use were still needed before possible inclusion of IAD in the addictive and related disorder category.

Different clinical descriptions and research findings suggest the existence of various types of Internet addictions. From a cognitive-behavioral perspective, Davis (2001) proposed two categories of problematic Internet use (PIU): "generalized PIU" (GPIU) and "specific PIU" (SPIU). GPIU refers to a multidimensional overuse of the Internet and SPIU refers to overuse in a specific area (e.g., online gaming). From this perspective, the Internet could be the facilitating vector for preexisting addictive disorders (e.g., gambling). Alternatively, it could be the vector for a new addictive behavior (e.g., chatting).[1]

IAD has also been conceptualized as a primary impulse control or obsessive-compulsive disorder (Yellowlees and Marks 2007) or as a comorbid condition (e.g., ADHD, anxiety, depression). This suggests that IAD could be a secondary disorder to some psychiatric conditions.

94.2 Epidemiological Data

One way to assess the stability of IAD as a disorder, and determine its prevalence, is to screen for it in the general population and specific samples. Lack of epidemiological studies and adult samples limits our understanding of the phenomenon. The major obstacle that the scientific community has faced in the last decade is the lack of validated and consensual screening tools. Prevalence rates of IAD are reported to vary from 2.7 % (Dong et al. 2010) to 20.9 % (Kormas et al. 2011) for 10–30-year-old Internet users. Similarly, they range from 3 % to 36.8 % (Zanetta Dauriat et al. 2011) for 10–54-year-old online video games. Furthermore, variation between countries (Durkee et al. 2012; Sun et al. 2012) suggests cultural factors may influence Internet use habits. This increases the complexity of evaluating IAD.[2]

[1]For further details, see "What Is Addictive in the Internet" section.

[2]For epidemiological data from the USA, Asia, and Europe, see Moreno et al. (2011) and Durkee et al. (2012).

The differences in IAD prevalence are due to differences in the samples studied but also to the variety of the assessment tools used. In a 28-month period (January 2010 to April 2012), 37 articles were published and indexed in PubMed, containing 14 different screening tools (Achab et al. 2012). The most frequently used (39 %) is the 20-item IAT (Young 1996). However, using the same tool (e.g., IAT), and focusing on similar student samples, variation in prevalence rates was still found (2.7–20.9 %). Gender characteristics and differences in IAD cutoff scores contribute to these disparities. Furthermore, variations on the focus of interest (i.e., general Internet overuse, video games, Internet-based sexual addiction, etc.) also affect prevalence figures. Finally, selection bias was found, with two thirds of the studies involving nonrepresentative samples of students.

These findings are supported by a recent review on PIU using the Strengthening the Reporting of Observational Studies in epidemiology (STROBE) criteria. Particularly Moreno et al. (2011) found weak internal and external validity of the concept when using epidemiological data from similar populations (i.e., US adolescents and college students).

94.3 Internet Addiction Screening Tools

A number of IAD screening tools are available. Screening tools have been found to strongly correlate with each other and also with self-reported Internet addiction (Achab et al. 2011; Widyanto et al. 2011). The theoretical construct underlying the development of IAD screening tools followed different models. (a) **The addiction model** is the basis for some tools that are adapted from **DSM IV substance dependence criteria**. For these tools, the word *substance* was substituted with *online activity* or *online video gaming* (DSM Adapted Scale for online video gaming (DAS) (Achab et al. 2011). (b) **The impulse control disorder model** is the basis for other tools adapted from **DSM pathological gambling criteria** [the Young Diagnostic Questionnaire (YDQ) and Young Internet Addiction Test (IAT)] (Moreno et al. 2011). Other tools were inspired by the (c) ***cognitive and behavioral PIU model*** (Davis 2001). This defines PIU as a four-dimensional entity consisting of diminished impulse control, loneliness/depression, social comfort, and distraction (Davis' Online Cognition Scale OCS) (Moreno et al. 2011). (d) The **PIU behavioral addiction model** is the basis for the Compulsive Internet Use Scale (CIUS) (Meerkerk et al. 2009). It also informs the Griffith Addiction Components Criteria (i.e., salience, mood modification, tolerance, withdrawal, relapse, and harm) (Moreno et al. 2011).[3,4] Other attempts to define PIU have included the amount of time spent online. However, this is not considered to be a necessary condition for IAD (King et al. 2013).

[3]Beard (2005) identifies the theoretical concepts underlying the IA assessment tools in his review.

[4]For a detailed review of Internet addiction assessment tools, translated versions, and further possible improvements, see King et al. (2013).

In summary, the IAD concept needs additional research. Studies should be methodologically comparable and focus on each area of Internet use (SPIU). They should also consider cultural differences. This is of great importance, given the possible implications of the phenomenon, and increased demand for clinical treatment (Kormas et al. 2011; Alavi et al. 2012; Tonioni et al. 2012).

94.4 IAD Determinants

The Internet provides a new lifestyle for the population by providing immediate and extensive information. It also enables interaction with others and/or software through a wide range of leisure activities. Individuals can interact in an unlimited and "anonymous" way. However, several negative aspects balance these positive ones. Particularly, the Internet can be overused as a maladaptive coping strategy. It may become a "vector of social reward," source of "displacement from offline to online social interactions" or "compensation strategy" for life difficulties (Shen and Williams 2011). Some aspects of psychopathology are associated with problematic Internet use such as personality traits and environment characteristics (Shen and Williams 2011).

Risk factors contributing to the development of PIU have recently been investigated (Tsitsika et al. 2011). Data on European college students suggests that young males who lack emotional and psychological support are more likely to demonstrate PIU (Durkee et al. 2012). Psychoticism was also linked to excessive Internet use in a recent study on Greek adolescents (Fisoun et al. 2012).

In addition to sociodemographic and psychological determinants, neuroimaging studies have been conducted. These demonstrate similarities between IAD and substance abuse disorders, suggesting there may be common neural substrates. Cue-induced craving for online activities, for example, has shown the same functional cerebral images as substance dependence (Ko et al. 2009). Similarly, reduced dopamine levels and glucose metabolism have been found in cerebral regions associated with impulse control and reward processing (Schoenbaum et al. 2003). Enhanced reward sensitivity and reduced loss sensitivity have also been reported (Dong et al. 2011a). These neural findings in IAD subjects give weight to the addictive spectrum theory.

In comparison with controls, people with IAD show impaired executive functions. This includes longer reaction times and a greater number of errors in a color-word Stroop task (Dong et al. 2011b). Poorer cognitive control has been reported (Dong et al. 2010). Delayed strategy learning is possibly more marked than in other addictive behaviors (Sun et al. 2009). However, compared to drug abusers and pathological gamblers, people with IAD demonstrate better response inhibition (Sun et al. 2009). Decision-making in college students has been found to improve in IAD subjects during a repetitive risky condition task (IGT).[5] This is reported to

[5]Iowa Gambling Task (IGT) tests the somatic marker hypothesis postulating that biasing signals, arising from neural emotional circuitry, influence reasoning. (Bechara and Damasio 2002).

be due to better implicit emotional learning skills, when compared to healthy controls (Ko et al. 2010). Further studies should investigate more precisely the cognitive and emotional mechanisms involved in IAD. They should also determine whether impaired cognitive skills are a preexisting condition or a secondary consequence of IAD.

In addition to functional impairments, structural cerebral changes have been reported in adolescents with IAD. These include a lower location for gray matter density (Zhou et al. 2011) and white matter abnormalities in the cerebral areas involved in working memory (Le Bihan et al. 2001).

From a longitudinal perspective, IAD has been alternatively conceptualized as (a) **temporary** (e.g., Internet novelty) (Kraut et al. 1998; Widyanto and McMurran 2004), linked to **stressful life events** (Armstrong et al. 2000) or a **dependent** phenomenon (Shek and Yu 2012), or as (b) a **persistent disorder** with underlying **personality traits** (self-reliance, emotional sensitivity, reactivity, vigilance, nonconformism, low self-disclosure) (Young and Rogers 1998). It may also meet certain needs (i.e., providing a sense of belonging and information for neurotic subjects and communication and relationships for extraverted subjects) (Amiel and Sargent 2004). Recent findings demonstrate the stability of IAD over time (1 year) for Asian adolescents. There were no demographic factors found that could predict the duration of the excessive behaviors. Given these findings, early interventions to treat problem Internet users appear important (Shek and Yu 2012).

Identifying long-term risk factors for IAD is also important in order to guide preventive healthcare and improve Internet governance policies.

94.5 IAD and Related Disorders

Excessive Internet use has been reported to correlate with numerous conditions including impaired social and professional functioning, some personality traits, and psychiatric disorders.

Family dysfunction or problems, poor academic performance, and limited hobbies have been found to be more frequent for teenagers with IAD (Huang and Leung 2009; Tsitsika et al. 2011). In adult samples IAD included a self-perceived negative impact on family, partners, work, emotional state, hobbies, sleep quality, friendships, and health (Achab et al. 2011; Bergmark et al. 2011). However, no longitudinal data currently exists on this. Comorbid psychopathology with PIU has received some scientific interest. Two recent reviews (Ko et al. 2012; Carli et al. 2013) summarize the published findings, the majority of which use Asian samples. In the cited studies, PIU was significantly associated with depression, ADHD, anxiety, obsessive-compulsive symptoms, and hostility/aggression. Surprisingly, PIU was not found to be correlated with social phobia (Carli et al. 2013). The strongest link was found between PIU and depression (Carli et al. 2013) (major depressive disorder, dysthymic disorder, and suicidal ideation). It is possibly linked to Internet-based perceived social support, escapism, achievement, and sense of control (Ko et al. 2012). The clinical results are

consistent with the common biological vulnerability found within depression and IAD (i.e., transporting serotonin polymorphism) (Wrase et al. 2006). The literature review also highlighted more ADHD symptoms in children and adults with IAD. Furthermore, a tendency to become addicted to the Internet was found for adolescents with ADHD. This could be explained by some Internet characteristics (e.g., rapid response, easier and delayed interpersonal relationships, immediate reward, multiple stimulating tasks). Such characteristics may serve to reduce boredom and provide stimulation and a sense of efficiency. However, the contribution of these potential gains is yet to be established. Methylphenidate showed possible efficacy in treating coexisting IAD and ADHD, in favor of possible common biological substrate (Ko et al. 2012). PIU was also associated with the presence of a hostility trait. Internet could be a means of expressing this personality trait or escaping from resulting interpersonal difficulties in the real world (Ko et al. 2012). An association was found between social anxiety symptoms and PIU. This is proposed to be due to online social support and avoidance of face-to-face interactions, provided by the Internet (Ko et al. 2012). One study (Yen et al. 2012) showed that symptoms decreased during online social interactions in comparison with offline interactions. This suggests that progressive exposure to social situations could be a suitable psychotherapeutic approach. Surprisingly in a recent systematic review of publications, no correlation has been found between PIU and social phobia, after controlling for confounding variables[6] (Carli et al. 2013). The cooccurrence of IAD and substance use disorders has been reported in some studies involving adolescents. However, the link remains unclear (problematic behavioral model, common neurocognitive substrates) and needs further research (Ko et al. 2012).

In summary, the causality and the evolution of disorders related to IAD are yet to be clearly established. Longitudinal studies using large and representative samples are required.

94.6 What Is Addictive About the Internet?

To understand what is addictive about the Internet, comparisons with substance addiction are useful. We can take the example of tobacco smoking. When people refer to a tobacco addiction, it is in fact the nicotine in the tobacco that is addictive. Therefore, we need to make some clarifications. When we speak about tobacco, the distinction should be made between:

1. Addictive products (nicotine)
2. First-order vectors: the carrier of the addictive substance (tobacco leafs)
3. Second-order vectors: the mode of consuming tobacco leaf (in cigarettes or pipes)

If we apply this distinction to the Internet, it helps to clarify the concept of Internet addiction. From this perspective, the Internet itself is simply a vector of addictive products. If we refer to our example, the computer or smartphone

[6]For a detailed review, see Carli et al. (2013).

(hardware) are the first-order vectors (the carrier of a product). Hardware has different characteristics which influence how or when a product can be used. This may be constant (smartphone), difficult to access (expensive Internet café in some countries), high-speed connection or not, etc. The software (online games, social networks) are the second-order vector.

If we want to understand what is addictive about the Internet, we have to identify the addictive product on the Internet. This product may be delivered in a more or less efficient manner. Using our example of tobacco consumption, some pertinent questions are as follows: Is it easy and cheap to find tobacco? How should it be consumed? (in a cigarette or chewed?) But these questions are relevant only if tobacco contains nicotine; without nicotine, no addiction process is possible.

To understand what is addictive about the Internet, specific stimuli that are available online need to be studied. Causes of behavioral addictions are now understood to be salient stimuli that trigger the reinforcement process (via the mesolimbic dopaminergic system). This leads to compulsive and automatic behaviors (Walter et al. 2005). Rewards generated by substance abuse are triggered by the neurobiological actions of the substance. This leads to an increase in the extracellular concentration of dopamine in the nucleus accumbens (Volkow and Li 2004). Increases in dopamine can also be achieved by nonpharmacological stimuli such as monetary rewards (Izuma et al. 2008). Similarly, this effect can be created by sexual stimuli, social acceptance, fairness, cooperative social interactions (Tabibnia and Lieberman 2007), social hierarchies, or humor. Internet software (the first-order vector) can contain varying amounts of salient stimuli. The intuitive idea that gaming or social networking software are more addictive than work software is true when looking at the amount of salient stimuli in these programs.

To be addictive, the presence of salient stimuli alone is not enough. The schedule of the rewards in terms of amount and frequency is crucial to the addictiveness of any stimuli. A parallel with gambling is useful here: The addictive properties of slot machine (fast-paced rewards, delivered in a reinforcing manner) are greater than those of a once-weekly lottery game, with low gain probability (Griffiths 1999). One theory that explains the addictive properties of Internet contents is operant conditioning (Skinner 1977). According to this theory, the likelihood of a specific behavior is increased or decreased through positive or negative reinforcement. Different types of operant conditioning exist, but the vast majority, found in Internet addictive components, are *variable-ratio schedules*: These arise when a behavior is reinforced after an unpredictable number of responses. Variable reinforcement schedules create a high steady rate of responding and are efficient for maintaining a behavior. This type of schedule is mostly seen in online role-playing games where repeated actions by an avatar can trigger a variable reward. An example is the repeated action of killing enemies in games. In World of Warcraft, the most popular massive online role-playing game, most of the actions involve defeating monsters. When a monster is defeated, the avatar gains a virtual reward. There are similarities, here, with the reward schedule used in slot machines. The avatar has a small chance of winning a rare item such as a powerful weapon. Winning this weapon can be compared to winning the jackpot in a slot machine, as

the probability of winning modest rewards (1X your bet in slot machines or a "standard weapon") is higher. Social network programs such as Facebook use the same mechanism. The whole structure of Facebook promotes certain behaviors or actions: posting comments, videos, and pictures and obtaining a reward (a number of friends answering to this post or liking this post). The number of comments or likes varies in terms of time and quantity. As mentioned before, the content of these comments is salient stimuli (positive social interactions, social acceptance).

In conclusion, the distinction between vectors and products helps us to be more accurate when defining an Internet addiction. Internet is then probably a vehicle of possible addictive products. The identification of specific stimuli and operant conditioning mechanisms present in the Internet product will predict their addictive risks. It is therefore not surprising that the contents of MMORPGs (first-order vector) are one of the most addictive products on the Internet as these contain numerous salient stimuli. Furthermore, rewards are mainly delivered on a variable-ratio schedule.

94.7 Treatment of Internet Addiction

Today there are many specialized clinic treatment programs which exist mainly in Asian countries. These are also found in Europe and English-speaking countries. The programs are often developed in association with dedicated gambling addiction programs. There are however limited publications on the efficacy of such treatments. The few existing publications (Khazaal et al. 2012) primarily relate to interventions inspired by cognitive-behavioral therapy (for details, see Table 94.1). Pharmacotherapy in Internet addiction has also known few scientific interest (Achab, Bertolini and Karila 2012).

A preliminary meta-analysis (Winkler et al. 2013) highlights the limited number of existing controlled studies. Findings highlighted a number of limitations such as absence of clear definition for the disorder treated and limitations of the instruments used. Moreover, there are omissions in the description of participants and inclusion processes. A further difficulty is linked to the wide diversity of Internet-related disorders. The Internet may amplify another primary addiction (sexual behaviors, purchasing, gambling). It can also be integral to the structural characteristics of a primary addiction (MMORPG-type video games). The vast majority of studies describe interventions for people presenting with a MMORPG addiction.

94.7.1 Nonspecific Approaches

Currently, the studies that have been published are based upon current techniques for addiction treatment. These include self-support concepts adapted from the 12 steps model, rehabilitation programs in residential setting, the motivational approach, cognitive-behavioral techniques to identify triggers and cognitive distortions, and psychoeducation for emotions (King et al. 2011, 2012). It is not often clear

Table 94.1 Psychosocial treatment for Internet addiction: open-label studies and controlled trials

Publication	Assessment	Method	Population	Treatment	Outcome	Effect size
Bai and Fan (2007) China	Chinese addiction scale – revised	Open-label study $N = 48$	College students Age: $m = 19$ 16.7 % women	Multilevel counseling model: CBT, social competence training, self-control strategies, communication skills (in group)	Reduction of Internet addiction symptoms	IA: 1.45
Cao et al. (2007) China	YDQ/Chinese addiction scale revised/screening for childhood related anxiety disorders	Open-label study $N = 57$	2,620 students from four middle schools of Changsha City were surveyed using YDQ Following clinical interview, students who met IA criteria were recruited	CBT	Reduction of emotional symptoms Reduction of addiction symptoms	IA: 1.09 Anxiety: 0.78
Du et al. (2010) China	Beard's Diagnostic Questionnaire	Randomized controlled trial $N = 56$	School students Age: $m = 12$–17 Met diagnostic criteria according to Beard's Diagnostic Questionnaire	Multilevel school-based intervention involving 8 sessions of group-based CBT	Reduction of Internet use and anxiety Improvement in time management Treatment gains observed at 6 months follow-up	Posttreatment IA: Cohen's $d = 1.08$ Follow-up (6 months) IA: Cohen's $d = 1.35$
Kim (2008) Korea	Korean Internet addiction	Controlled trial $N = 25$	University student Volunteers from a sample of 32 Internet addicts who were screened	Group counseling Reality therapy (5 weeks)	Reduction of Internet addiction symptoms Increase in self-esteem	Not reported
Lanjun (2009) China	Internet addiction scale, State-trait anxiety inventory for adults	Open-label study $N = 70$	College students 45.71 % women	Multilevel counseling model: CBT + sport	Reduction of anxiety Reduction of addiction symptoms	IA: 2.98 Anxiety: 0.43

Li and Dai (2009) China	Chinese Internet addiction scale	Controlled trial $N = 76$	Adolescents 10.53 % women	CBT (individual)	Reduction of addiction symptoms	IA: 1.46
					Reduction of anxiety, depression, and compulsions	
Orzack et al. (2006) US	Orzack Time Intensity Scale (OTIS)	Open-label study $N = 32$	Men age: $m = 26$–59	Multilevel counseling model: CBT, readiness to change, motivational interviewing	Better quality of life	Time: 0.27
	Beck Depression Inventory		Involved in Internet-related problematic sexual behavior		Reduction in depressive symptoms; patients with comorbid anxiety/mood disorders responded best to treatment	Depression: .35
Su et al. (2007) China	Young Diagnostic Questionnaire (YDQ)	Controlled trial $N = 65$	University students recruited from a university in Beijing	Self-help (3 types)	For all groups	YDQ: Cohen's $d = 0.72$–0.82
			Voluntary screening with YDQ ($N = 91$) – participants: classified as "dependant" or "at risk" according to YDQ or being online for more than 14 h per week		Reduction of addiction symptoms	
					Reduction in hours spent online	Online activity: Cohen's $d = 0.75$–0.98
Young (2007) US	YDQ Hamilton depression scale	Open-label study	Clients seen through the "Center for Online addiction" screened using the IAT	CBT (12 sessions)	Reduction of clients' thoughts and behaviors related to compulsive Internet use	IA: 0.93 Time: 2.38
			42 % women		Gain observed at 6 months follow-up	
			Age: $m = 38$ for men			
		$N = 114$	$m = 46$ for women			

IA Internet addiction, *CBT* cognitive-behavioral therapy

whether individual or group interventions have been used. When Internet use arises as part of another addiction, the clinical approach focuses on that domain (see chapters VII-3, VII-6, VII-8). There has also been an emergence of Internet-based therapeutic programs (Su et al. 2011). These can be a suitable gateway to care for intensive electronic media users (Zematten et al. 2010).

94.7.2 Treatment of Comorbidities and Pharmacological Approaches

Two pilot studies have investigated methylphenidate and bupropion for people with a MMORPG addiction. At posttest (6–8 weeks), a reduction in the length of gaming sessions in addition to a reduction in cue-induced brain activity was observed (Han et al. 2009, 2010). However, the study on methylphenidate included a population with ADHD and also included a high dropout rate. The study on bupropion excluded subjects with a comorbid axis I diagnosis. In practice, so far, no medication has received accreditation for the treatment of behavioral addictions. In clinical practice, the indication of pharmacotherapy is then based on the presence of possible comorbid disorders such as symptoms anxiety or mood disorders (Ko et al. 2012).

94.7.3 Cognitive-Behavioral Approach for Family Members and Significant Others

To our knowledge, a single randomized study has been published for family approach of Internet addictions (Du et al. 2010). The study focused on young adult online players. A multimodal behavioral intervention for groups was evaluated. The program emphasized communication techniques and management of triggers, alongside parents monitoring their children's emotions. It also included problem-solving techniques and practical advice for parents on limiting home Internet use. In addition, an electronic media awareness program for relevant school professionals was implemented. When compared to the control condition, a significant reduction in Internet use was observed at posttest and maintained at 6 months follow-up. A lasting reduction in anxiety and improved time management were also observed.

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Internet Gaming Addiction: The Case of Massively Multiplayer Online Role-Playing Games

95

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Contents

Abstract

Internet gaming disorder is one of the main types of Internet-related disorders. Recently, and despite inconsistencies in classification and limited data regarding the etiology of the condition, Internet gaming disorder has been included in Sect. 3 (research appendix) of the DSM-5. The focus of the current chapter was the dysfunctional involvement in a specific type of video game which has some inherent characteristics reinforcing its addictive nature: Massively Multiplayer Online Role-Playing Games (MMORPGs). MMORPGs are indeed one of the most recent and popular types of video games played worldwide, and problematic and uncontrolled involvement in playing MMORPGs is the most frequently reported activity by people seeking help for an Internet-related problem. In this chapter, we first described the specific structural characteristics of MMORPGs

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themselves (e.g., permanent world, reinforcement schedule, advancement systems, interface favoring social exchanges) and explained how they can increase their "addictive potential". Then, the main psychological factors (motives to play, impulsivity traits) were reviewed alongside neurobiological features (e.g., changes in neural circuitry involved in controlled regulation of behavior and reward drive) related to the development and maintenance of MMORPG addiction. The few available studies having tested the efficacy of treatments targeting Internet and video game addictions were also briefly considered. Limitations of existing data are emphasized, and avenues for further research proposed (both at the theoretical and clinical levels).

95.1 Introduction

There is growing evidence to support the claims that the use of the Internet can become dysfunctional and cause negative impact in daily living and has given birth to the construct of "Internet addiction." Internet addiction is generally considered as an addictive disorder that shares most features of drug addictions (i.e., salience, craving, tolerance, loss of control, mood modification, withdrawal, relapse). Over the last few years, there have been a number of calls to incorporate Internet addiction as a new diagnostic category in the next edition of the DSM. However, the DSM-5 task force recently decided that there is not enough empirical research to warrant inclusion of "Internet addiction" as a new psychiatric disorder in the DSM-5.

The validity of the Internet addiction construct is challenged by theoretical and empirical concerns. Internet addiction is indeed an umbrella construct that encompasses a variety of different dysfunctional behaviors related to the involvement in online activities that do not necessarily coexist (e.g., video game playing, cybersex, social networking, online gambling, etc.). Nevertheless, the empirical evidence regarding the risk factors that are shared among cyber addictions (i.e., factors implicated in the etiology of all cyber addictions) from those that are specific (i.e., factors implicated in the etiology of a specific cyber addiction, e.g., online gambling) is scarce. Another concern is raised by the elevated comorbidity rates between cyber addictions and other psychiatric disorders, which implies that cyber addictions can be either primary or secondary disorders (e.g., resulting from a depressive disorder) (Gentile et al. 2011).

Recently, and notwithstanding inconsistencies in classification and limited data regarding the course and the etiology of the condition, **Internet Gaming Disorder** has been included as a new clinical entity in Sect. 3 of the DSM-5 (Petry and O'Brien 2013). The goal of this section is to foster research on the conditions included therein. In this context, the current chapter focuses on the dysfunctional involvement in a specific type of video game which has some inherent characteristics reinforcing its addictive nature: Massively Multiplayer Online Role-Playing Games (MMORPGs). Problematic and uncontrolled involvement in playing MMORPGs is indeed the most frequently reported activity by people seeking help for an Internet-related problem (e.g., Thorens et al. 2013).

95.2 Massively Multiplayer Online Role Playing Games (MMORPGs)

95.2.1 Structural Characteristics of MMORPGs

MMORPGs are one of the most recent and popular types of video games played worldwide. An estimation of the total number of MMORPG players around the world is 20 million. MMORPGs are a type of computer role-playing game in which a large number of players interact with one another in a **persistent** virtual world – an environment that exists independently of the players. Consequently, both events and interactions between other players occur while the user is absent from the persistent world. In MMORPGs, players assume the role of a fictional character (often in heroic-fantasy-based worlds such as the one depicted by writer J. R. R. Tolkien in the saga "*Lord of the Rings*") and take control of many of that character's actions. Character creation typically involves various components such as the selection of an avatar (i.e., a visual representation of the character in the virtual world) but also specific skills and attributes that define the character (e.g., gender, race, profession, physical aspects). The concept of **advancement** is a fundamental characteristic of playing MMORPGs, implying that a user's character will acquire new powers, skills, and items (i.e., objects that can be found in the game, such as a special weapon or gold pieces) as rewards for succeeding in certain missions or quests (e.g., defeating an opponent or exploring a special place in the virtual world). Another important feature of playing MMORPGs is **social interaction**. It is indeed possible, when playing, to communicate easily with other players (written chat or audio). Furthermore, players can also regroup themselves in virtual social networks named guilds, which are persistent hierarchical organizations of characters with common objectives and backgrounds. Each guild has its own rules and users who want to be enrolled generally need to present their motivations and proofs that their characters meet the guild's requirement. These abovementioned specificities (permanent world, advancement and reinforcement system, social interactions aspects) have been proposed as **structural characteristics** reinforcing the addictive nature of this specific type of video game (e.g., King et al. 2010). It has, for example, been shown in a longitudinal study by Smyth (2007) that MMORPG players, in comparison to other types of video game players (e.g., arcade, console or solo-computer players), reported significantly more hours spent playing, worse health (e.g., more cigarettes smoked, less physical exercise, worse sleep quality, etc.), and greater interference in real-life socializing and academic work at a 1-month follow-up. This finding was confirmed in a recent cross-sectional study by Kuss et al. (2012) that emphasized MMORPG players (compared to those playing other types of video games) more often displayed signs of dysfunctional use. In the last years, a growing number of studies have focused on problematic involvement in video games and more particularly in the playing of MMORPGs (see Kuss and Griffiths 2012a, for a review). Most of these studies, which have considered dysfunctional use within the framework of "behavioral addictions", tried to identify the **psychological factors** and/or the **neurobiological correlates** involved in its development and maintenance.

95.2.2 Psychological Factors

Two types of psychological factors have been extensively investigated in relationship to MMORPGs overuse: (1) motives to play online and (2) individual differences in self-control.

Recent research on MMORPGs revealed that an individual's motivations for playing have an important role in the onset of online game involvement and in its continuation (Billieux et al. 2013; Yee 2006). A critical step regarding the comprehension of players' motives resulted from the work of Yee (2006) who explored players' motives through an online survey including 3,000 users of *World of Warcraft* (currently the most popular MMORPG worldwide). Yee's study revealed the existence of three broad types of motivations, namely, the achievement motive, the social motive, and the immersion (in a virtual world) motive. Each of these broad motives can actually be divided into subcomponents (e.g., the social factor comprises separate motives such as liking socializing while playing, playing to create new relationships, or seeking to solve problems through teamwork). A growing number of studies tried to identify motives to play online that predict the involvement in dysfunctional online gaming based on Yee's model of players' motives (e.g., Billieux et al. 2011, 2013; Kuss et al. 2012; Yee 2006). On the whole, these studies revealed that specific achievement- and immersion-related motives are strong predictors of problematic online gaming (as reflected by scales measuring symptoms of addiction and impact in daily life). Regarding achievement-related motives, problematic use was consistently associated with "advancement" (i.e., the desire to gain power, progress rapidly, and accumulate in-game symbols of wealth or status) and "mechanics" (i.e., interest in analyzing the underlying rules and system in order to optimize character performance). Regarding immersion-related motives, systematic relations were highlighted with "escapism" (i.e., the need to play to avoid thinking about real-life problems). The "role-play" component of the immersion motive (i.e., the aspiration to create a character with a background story and to interact with other players according to it) was also related to problem gaming, although the size of the highlighted associations was smaller ($r < 0.30$). In contrast, the available studies based on Yee's model consistently emphasized that social-related motives (e.g., playing to meet people or teamwork) are not related to problematic use. These data sustain that dysfunctional engagement in MMORPGs can either result from an uncontrolled drive to look for achievement in the game or be the consequence of a maladaptive strategy used to cope with negative affect (e.g., boredom, anxiety, dysphoria). This assumption has recently received support by a study of Billieux et al. (2013) using *avatar* monitoring techniques (i.e., measuring behaviors made by players in the virtual world by their character). Results of the study indeed highlighted that the escapism motive is unrelated to actual in-game behaviors, as well as to progression in the game (measured through an 8-month avatar monitoring), implying that escapers play to be immersed in a virtual reality more than to reach specific objectives in the game. In other words, it can be postulated that for certain problematic players, the game is used as a kind of dissociative technique to escape real life.

A large body of evidence tied dysfunctional video game use (and more largely Internet-related disorders) to poor self-control (e.g., traits of impulsivity and sensation seeking, lack of inhibitory control, impaired decision-making, reward drive) (see Billieux and Van der Linden 2012, for a review about Internet-related disorders and self-regulation).[1] This focus on self-control and impulsivity lies in the fact that dysfunctional video game involvement is most of the time conceptualized as an addictive behavior and that uncontrolled use is a key symptom of this disorder (King et al. 2013).

Several studies have highlighted that video game addicts have higher levels of self-reported impulsivity. In particular, a study by Gentile and colleagues (2011) found in a 2-year longitudinal study that greater impulsivity acts as a risk factor for the development of problematic use of video games. Impulsivity is however an umbrella construct that encompasses a combination of multiple and separable psychological dimensions. In the last decade, a growing number of researches supported a model that clarifies the multidimensionality of impulsivity by subdividing it into four dimensions, which are related but also specific (the UPPS model of impulsivity; Whiteside and Lynam 2001). These four dimensions are defined as follows: urgency, the tendency to act rashly when experiencing intense emotions (both positive and negative); premeditation, the tendency to take into account the consequences of an act before engaging in that act; perseverance, the capacity to remain focused on a boring and/or difficult task; and sensation seeking, the tendency to enjoy and pursue new and exciting activities. Notably, a growing number of studies have highlighted specific links between these impulsivity facets and various psychiatric disorders (e.g., substance abuse, problem gambling, compulsive buying, suicide ideations and attempts, aggressive behaviors). Recent studies showed that problematic MMORPG involvement (measured with scales assessing addiction symptoms, such as loss of control, as well as with the related impact on various spheres of daily life) is firstly predicted by the urgency facet of impulsivity (when controlling for other impulsivity components), although relationships with low premeditation and perseverance were also emphasized (Billieux et al. 2011, 2014). In contrast, the sensation-seeking facet of impulsivity was inconsistently related to problematic MMORPGs use (and more largely Internet overuse). A potential explanation for the absence of a systematic relationship between sensation seeking and dysfunctional MMORPGs use is that the questionnaires targeting this impulsivity component probably do not assess how people seek stimulation and rewards through online game involvement.

Recent evidence suggests that the various facets of impulsivity are related to specific psychological executive and motivational mechanisms involved in the regulation of behaviors. More precisely, it has been emphasized that three of the dimensions of impulsivity (urgency, lack of premeditation, lack of perseverance)

[1] See Billieux and Van der Linden (2012) and Kuss and Griffiths (2012a) for comprehensive lists of publications having investigated self-regulation-related constructs in Internet and video games addictions.

are related to executive mechanisms underlying self-control abilities (e.g., inhibitory control, decision-making abilities, resistance to cognitive interference), whereas the last dimension (sensation seeking) rather depends on motivational mechanisms related to reward sensitivity and approach tendency. Behavior thus depends on the interaction of controlled (conscious) processes with automatic processes (less conscious). For example, when faced with a critical internal or external stimulus (e.g., a cybercafé, an unexpected pop-up related to an online game, an emotional state), a MMORPG player is susceptible to experience intrusive thoughts and/or craving about the game, which can automatically trigger the approach motivational system involved in reinforcement seeking. In such a situation, the capacity of this player to exert self-control (e.g., voluntary inhibiting the gaming behavior) will depend on the effectiveness of its controlled (or executive) processes. These last years, a few studies highlighted that video game addicts (in comparison to matched control participants) are characterized by impairments in a specific executive mechanism involved in self-control, namely, the ability to suppress prepotent responses (e.g., Littel et al. 2012). Furthermore, it was also demonstrated that individuals having dysfunctional involvement in MMORPGs display poor decision-making ability (e.g., Pawlikowski and Brand 2011). Although these studies shed some first light on the self-control deficits involved in uncontrolled MMORPGs use, further studies are required to confirm and strengthen the findings, as well as to explore other mechanisms involved in self-regulation (e.g., reinforcement learning, resistance to cognitive interference).

Other potential psychological factors involved in the etiology of online game addictions have been considered, although they remain currently less investigated than the factors mentioned above. For example, individual differences in self-esteem (i.e., the extent to which individuals view themselves as likeable and worthy) predict the involvement in online games. Several studies indeed revealed associations between a low level of self-esteem and symptoms of MMORPG addiction (e.g., Billieux et al. 2014), which suggests that excessive playing can serve to approach a more ideal virtual self by avoiding the actual self. Another line of research focused on the potential role of schizotypal personality (and related manifestations such as delusions) in the onset of excessive involvement in Internet-related activities, including MMORPGs (e.g., Mittal et al. 2013). Although preliminary, these studies suggested that schizotypy-related behaviors can promote the development and the perpetuation of over involvement in online games. Further research is thus required to extend our comprehension of the various psychological mechanisms (and their interactions) in the etiology of online game addictions.

95.2.3 Neurobiological Factors

A number of neurobiological factors have been found to be associated with Internet and online gaming addiction. In a recent systematic literature review, Kuss and

Griffiths (2012b) found that in eighteen empirical studies,[2] neuroimaging has been used in order to elucidate Internet and gaming addiction against the background of more traditional substance-related addictions. State-of-the-art neuroimaging techniques have been used in the included studies, namely, electroencephalograms (EEG), positron emission tomography (PET), single-photon emission computed tomography (SPECT), as well as functional and structural magnetic resonance imaging (fMRI and sMRI). With EEG, brain activity in the cerebral cortex is assessed. PET measures the level of positively charged electrons in the brain which provides an indicator for metabolic neuronal activity, whereas SPECT measures neuronal activity following the injection of radioactive tracers. With fMRI, brain blood oxygen levels are quantified in order to demarcate regions of activity. Finally, sMRI images brain structure, using methods such as voxel-based morphometry (VBM) and diffusion-tensor imaging (DTI).

Using these neuroimaging techniques, the systematic literature review revealed that Internet and gaming addiction are in no way inferior to substance-related addictions on three levels. On a biochemical level, frequent engagement in online and gaming activities has been shown to alter neuronal dopamine levels via reductions in dopamine transporter availability. This may lead to molecular dysfunctions in the dopaminergic system. On the level of neural networks, brain alterations appear as a result of excessive engagement with the Internet and online games. The brain adapts to the perpetual reinforcing stimulation and in turn becomes desensitized to natural reinforcers and thus needs more of the former, putting in motion a vicious cycle. The studies show that the function and structure of the orbitofrontal cortex gyrus changed as a consequence of excessive Internet use and gaming. The latter becomes more salient for the users who lose control over their behaviors. They have learned to use the Internet and games compulsively to recreate neuronal homeostasis. Finally, studies combining neuroimaging and behavioral techniques confirmed that people suffering from Internet and gaming addiction develop a number of cognitive deficits, including impairments in executive and attentional controls. However, on the bright side, a number of skills are advanced in this group. Studies indicate that the integration of perceptual information to the brain via the nervous system is facilitated, and hand-eye coordination is improved (Kuss and Griffiths 2012b).

In sum, state-of-the-art neuroimaging research offers compelling evidence for the similarities between Internet and gaming addiction with substance-related addictions. From the cited review, it appears that Internet and gaming addiction can be classed as behavioral addiction as the former fulfills a variety of characteristics that typify addictions. Correspondence between addictions exists on a molecular, neurocircuitry, and behavioral basis, indicating the addiction may best be conceptualized as a syndrome with common etiology, but different manifestation (Shaffer et al. 2004).

[2]For a detailed listing and evaluation of included empirical studies, refer to the original systematic review paper (Kuss and Griffiths 2012b).

95.2.4 Treatment of MMORPG Addiction

Internet addiction in general and addiction to playing MMORPGs are relatively new clinical phenomena. Consequently, research on their treatment is limited. However, a couple of systematic studies with the goal of evaluating treatment effectiveness have been published (King et al. 2011; Liu et al. 2012). Each of these is briefly outlined.

King et al. (2011) made use of the gold standard of clinical trial evaluation, the CONSORT (Consolidated Standards of Reporting Trials) statement (Schulz et al. 2010), in order to evaluate Internet addiction treatment studies (including MMORPG addiction). The CONSORT statement sets out a number of quality indicators for pharmacological and non-pharmacological clinical trials, such as transparence in justifying and reporting study methodology. These include stating eligibility criteria for participants, description of respective treatments, and a power analysis for the utilized sample size (Schulz et al. 2010). Only eight studies[3] met the established criteria, including one randomized controlled trial. The included studies differed significantly in design, definition, and assessment of Internet addiction, treatment, follow-up assessments, randomization and blinding, sampling, and recruitment. As regards treatment, it was particularly varied ranging from cognitive-behavioral therapy (CBT), motivational interviewing (MI), reality training, and individually designed therapy including psychological and or counseling elements. Overall, treatment was provided by trained professionals or via especially developed computer programs, lasting between one session and 19 months in total (King et al. 2011).

For their empirical review, Liu et al. (2012) selected Internet addiction outcome studies based on whether they reported treatment outcomes, included young Internet addiction patients aged 9–23 years, and were carried out in China, resulting in a final sample of 24 studies.[4] In order to evaluate these studies, criteria from the CONSORT statement were adopted including objectivity, sample size, power, outcome, randomization, active comparison, baseline, manualization, treatment adherence rating, collateral report, objective measures, intention to treat (ITT) analysis, and blinding. In terms of the outcome, more than half of the included studies were considered "methodologically strong" in sequence generation and ITT analysis, however weak with regard to the remaining criteria. With regard to treatment approaches, exercise programs, cognitive-behavioral therapy, electroacupuncture, family therapy, group-based treatment, motivational interviewing, and psychotropic medication were used most commonly, with over 50 % of studies using multimodal techniques. On average, the effect size was high (i.e., 1.89), suggesting that Internet addiction therapy is efficacious; however, the quality of the results was found to be low. The highest effect size was found for the most prominent multimodal treatment, CBT combined with psychopharmacotherapy, i.e., 3.93, attesting to its efficaciousness (Liu et al. 2012).

[3]For a detailed description of the included studies, please refer to the original review paper by King et al. (2011).

[4]A detailed description of studies is provided in Liu et al. (2012).

From the reported reviews of treatment studies, it appears that there is no single standardized evidence-based Internet addiction treatment available to date. The treatment studies published to date offer a wide range of therapy approaches, using dissimilar diagnostic criteria and heterogeneous treatment delivery. Taken collectively, more treatment research that fulfills high-quality standards is available in the Chinese-speaking rather than English-speaking world, indicating that the problem of Internet and MMORPG addiction may be more pressing in the former. From the few studies to date, it appears that a combination of CBT with pharmacotherapy yields the most promising results. The first cognitive-behavioral therapy manual for the treatment of computer game and Internet addiction has now been published in Germany (Wölfling et al. 2013). It combines group with individual therapy sessions on an outpatient basis. The manualization of Internet and MMORPG addiction treatment may be taken as first step toward the adoption of established clinical protocols, which will benefit managing risks, implementing research findings promptly, and standardizing treatment that is more cost-effective and efficient in the long run.

95.3 Conclusion

This chapter focused on a specific disorder of the spectrum of cyber addictions, namely, the dysfunctional involvement in MMORPGs. Having explained how some specific structural characteristics of the games themselves (e.g., permanent world, reinforcement schedule, advancement systems, interface favoring social exchanges) increase their "addictive potential," the main psychological factors (motives to play, impulsivity traits) were reviewed alongside neurobiological features (e.g., changes in neural circuitry involved in controlled regulation of behavior and reward drive) related to the development and maintenance of MMORPG addiction. The few available studies having tested the efficacy of treatments targeting Internet and video game addictions were also briefly reviewed.

In concluding, it is also noteworthy to mention some key points that should be taken into account both in clinical practice and empirical research:

- The empirical bases available to support the existence and exact nature of video game addictions (and other cyber addictions) are still scarce in comparison to those existing for substance addiction and some other behavioral addictions (e.g., pathological gambling). Empirical data about treatment efficacy is clearly lacking; however, the demand for treatment is likely to increase (e.g., Thorens et al. 2013).
- Video game addictions (and other cyber addictions) can be either primary or secondary disorders. Among other things, this implies that the prevalence rates reported in the literature are most likely overestimated and/or not representative of a specific disorder (e.g., sexual addiction versus online game addiction) and that the symptoms identified are not necessarily related to the postulated disorder.

- The studies now being carried out are becoming better both methodologically (e.g., development of in-game tracking techniques) and theoretically (e.g., development of psychological models of problematic use) although there is still a heavy reliance on self-selected samples. Further studies should thus focus on the recruitment of more representative samples.
- Recent studies challenged the demographic characteristics regarding individuals involved in playing online video games. First, this activity is no longer just a male adolescent or preadolescent activity, and online games are now also played by adults. The mean age of MMORPG players in many recent studies is often between 25 and 30 years old. In addition, it appears that there is an increasing feminization of gaming with more girls and women becoming gamers.
- The gaming studies field needs to develop better instrumentation to assess the symptomatology and prevalence of MMORPG addiction with sufficient specificity and sensitivity. In addition to diagnostic tools (i.e., scales used to differentiate problematic and non-problematic gamers), it would also be necessary to develop instruments that allow multidimensional scoring (e.g., loss of control, withdrawal, conflict, craving, compromised time control, hedonic aspects, mood regulation). Indeed, available studies often provided limited comprehension of the factors involved in the etiology of MMORPG addiction (e.g., personality traits, motives), as they have too often been conducted without considering its multifaceted nature. For example, a study designed to elucidate the role of self-regulation in dysfunctional online game symptomatology would benefit from using a scale able to measure aspects such as loss of control or pleasure seeking (psychological mechanisms or processes) as separate from aspects such as negative impact upon daily living (outcomes of the problematic behavior).
- Although MMORPGs appear to be more attractive video games when compared to "stand-alone" console-type games (due to structural characteristics such as 24/7 availability mentioned above), other less researched genres of online gaming (such as Real Time Strategy Games and First Person Shooters) may also require similar consideration in the future.

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Compulsive Buying Disorder

96

Tatiana Zambrano Filomensky and Hermano Tavares

Contents

Abstract

The increasing availability of credit has made buying a frequent behavior in everyone's life. Compulsive buying disorder (CBD) is characterized by loss of control over buying, accruing debts, and psychosocial distress. Reported by the founding fathers of modern psychiatry, Kraepelin and Bleuler described it as a monomania and named it oniomania. CBD may have a profound impact upon both individuals and society; however, it remains absent from current diagnostic classifications. There are still doubts regarding the psychopathology and nature of CBD; some regard it as a behavioral addiction or a member of two different groups, either the bipolar spectrum or the obsessive-compulsive spectrum of

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disorders. Conservative estimates describe a prevalence around 2 % in the general population with an extra 6 % at risk for CBD. An association with female gender is usually described, but it has been recently challenged. The CBD construct is based upon three concepts: emotional activation, urges, and affect regulation. Current and lifetime psychiatric comorbidities are usual among treatment-seeking compulsive buyer, respectively, 50 % and 90 %; the most common are mood, anxiety, and impulse control disorders. Accounts of subtypes of CBD patients describe a thrill- and pleasure-seeking impulsive type and an emotionally stricken compulsive type. SSRIs in general and citalopram in particular have been used to treat CBD, but so far, its efficacy remains undetermined. The modulation of dopamine pathways within the brain reward system has been speculated as a promising pharmacological approach. So far, the best evidence-based treatment approaches come from cognitive-behavioral models.

96.1 Introduction

Since antiquity, the act of buying has been present in society. The emergence of currency modified cultural and moral values, marking a period in which power went from being determined by the family name to being defined by commerce, gaining momentum with the adoption of monetary systems (Vissering 2008). The act of buying continued to distract and enrapture people throughout the subsequent millenniums, driving commerce and influencing governmental structure. The lack of control over this behavior aroused the concern that we could be facing a clinical disorder.

Compulsive buying disorder (CBD) was described at the beginning of the twentieth century by two descriptive psychiatrists, Kraepelin (1915) and Bleuler (1924). Both founded their descriptions on Esquirol's (1838) concept of monomania. Kraepelin (1915), the first to elaborate the syndrome, titled it oniomania – from the Greek *onios* (for sale) and *mania* (insanity), describing it as a pathological impulse. He underscored the predominance of the female sex and believed that oniomania would be a subclinical variation of kleptomania. Bleuler (1924) emphasized the impulsive nature of the disorder and likened it to the insanities of impulse along with pyromania (apparently much more abundant at that period that it appears to be today) and kleptomania (Tavares et al. 2008).

CBD did not arouse the interest of researchers in the following decades, except among the study of consumer behavior (O'Guinn and Faber 1989; Elliott 1994) and psychoanalysts that elaborated case reports (Krueger 1988). During the early 1990s, three independent clinical case series studies involving 90 individuals were published, after which CBD once again returned to be globally discussed (Christenson et al. 1994; Schlosser et al. 1994), with reports originating from countries such as Germany (Scherhorn et al. 1990), Brazil (Bernik et al. 1996), Canada (Valence et al. 1988), France (Lejoyeux et al. 1997),

England (Elliott 1994), and the USA. This renewed interest was probably fostered by the perception of the profound impact that CBD may have upon individuals as well as on society. Indeed, it is estimated that in the USA compulsive consuming generates more than US$4 billion in annual purchasing (Kacen and Lee 2002; Tavares et al. 2008).

Despite being described by researchers and scholars for more than a century, CBD continues to be, inexplicably, undefined and understudied. It is absent from modern classifications in psychiatry, except possibly for the classification in the residual category of Impulse Control Disorders Not Otherwise Specified in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (APA 2000) or the International Classification of Diseases of the World Health Organization, 10th Edition (ICD-10) (Filomensky et al. 2012). A possible explanation for this state of affairs is the existence of diagnostic doubts regarding the psychopathological nature of CBD. Some researchers consider CBD to be an addictive disorder, incorporating it into the classification of drug and alcohol abuse disorders, or behavioral addictions, which include pathological gambling, kleptomania, Internet addiction, and compulsive sexual behavior (Glatt and Cook 1987). Others consider CBD to be an excessive behavior secondary to mood disorders, associated within the frameworks of mania, hypomania, or mixed episodes in bipolar disorder (Lejoyeux et al. 1996), or as a subsidiary symptom of hoarding, on the obsessive-compulsive disorder spectrum (Hollander et al. 1996; Filomensky et al. 2012).

There is also a stream of researchers who criticize the attempts to classify compulsive consumption as a disorder, stating that it implies medicalization of variations within the spectrum of consuming behaviors (Lee and Mysyk 2004). Unfortunately, this view ignores the reality that CBD is a prevalent and severe syndrome and stigmatizes the attempts to recognize, understand, and treat the condition.

96.2 A Biopsychosocial View of Compulsive Buying

96.2.1 Epidemiology

Studies estimating the prevalence of CBD in the general and specific populations report rates of approximately 2–8 %. In spite of the increasing scientific and layman interest in the disorder, there is no evidence to suggest that the prevalence of CBD is increasing. A study by Faber and O'Guinn (1992) selected 292 Americans from the general population in Illinois to respond to the Compulsive Buying Scale (CBS) estimated that almost 6 % of the population would be at risk for CBD. Grant et al. (2005) evaluated 204 psychiatric inpatients and reported a prevalence rate of CBD over the lifetime of 9 %. More recently, a study by Koran et al. (2006) interviewed approximately 2,500 American adults through an anonymous telephone questionnaire. They determined a CBD prevalence rate of about 5 %, and a ratio of men to women of 1:1, which indicates a rather larger participation of men than previously reported. The anonymous nature of this telephone survey may have

helped male compulsive shoppers to be open about their difficulties. Indeed, other reports that pointed to male-to-female ratio around 1:4–1:5 were almost all conducted in clinical settings (Filomensky et al. 2012). Kraepelin and Bleuler had already proposed the predominance of the female gender in CBD, suggesting that the female compulsive buyer was in search of risk and excitement, much like the risk-seeking behavior in pathological gambling predominantly seen among men. For Dittmar and Drury (2000), the prevalence of the female gender in CBD appears as a compensation strategy to combat negative emotions and low self-esteem. They state that the gender difference is genuine and should not be attributed to the underrepresentation of males in clinical samples, basing their conclusion in a study conducted in the general population of the UK, in which 92 % of the respondents classified as compulsive buyers were women. Interestingly, in 2005 Dittmar carried out another survey about consuming behaviors in adolescents. Two-hundred and five teenagers between the ages of 16 and 18 were selected from two schools in England. The results indicated a CBD prevalence ratio similar to the adult survey, but without gender imbalance, suggesting that regarding uncontrolled shopping men are likely to catch up with women in the near future (Dittmar 2005). Nonetheless, gender differences regarding favored purchasing will likely remain, with female compulsive shoppers targeting mainly clothes, handbags, shoes, perfumes, makeup, and jewelry, while men prefer electronics and objects that display elevated social status such as expensive suits, watches, electronic gadgets, and cars (Christenson et al. 1994; McElroy et al. 1994; Black 1996, 2001).

It is believed that CBD begins toward the end of adolescence, around 18 years of age, or at the beginning of adulthood. This is the period in which the adolescent develops more autonomy and emancipation from the nuclear family, when they are likely to acquire credit for the first time (Black 2001). Nevertheless, the perception of buying behavior as a problem occurs later, around 30 years of age, and treatment seeking between 31 and 39 years of age.

Before 18 years of age, uncontrolled buying is generally associated with a more diffuse general pattern of behavioral disinhibition, which can include smoking, alcohol and drug misuse, and premature sex (Roberts and Tanner 2002). Besides, 24-h shopping made possible by online credit card purchasing could be a contributing factor to adolescent onset. Indeed, it has been reported that among computer compulsive users, up to 19 % would fulfill the criteria for CBD (Black 2001). In view of this fact, it is likely that some compulsive shoppers will enter their adult lives already with a substantial debt.

CBD is commonly associated with severe personal impairment, both financial and familial (Black 2001), as well as other psychiatric disorders, including personality disorders (Black 2007; Tavares et al. 2008). Although there are a lack of longitudinal studies for CBD, some studies indicate that the course of the disorder can be chronic or recurrent (Christenson et al. 1994; Schlosser et al. 1994). However, the treatment of CBD can modify the course of the disorder, as shown in a study in which patients who responded to treatment with citalopram maintained states of remission during 1 year (Koran et al. 2003; Aboujaoude et al. 2003).

96.2.2 Diagnosis and Assessment Scales

In 1989, O'Guinn and Faber defined compulsive buying as an addictive behavior characterized by "a response to an uncontrollable drive or desire to obtain, use or experience a feeling, substance, or activity that leads an individual to repetitively engage in a behavior that will ultimately cause harm to the individual and/or others (p. 148)," underscoring the chronic and repetitive nature of CBD. Valence and colleagues (1988) proposed that CBD was a three-pillar construct defined as follows: (1) a strong emotional activation when exposed to a shopping environment and shopping opportunities, (2) tension and buying urges elicited by the exposure to such stimuli, and (3) shopping and buying as means to obtain affect regulation, shortly lived because it is usually followed by post-purchase guilt. Moreover, it is likely that later negative consequences (indebtedness, family and friends reproaches, etc.) enhance the negative affective state, which in turn will lead to stress relief-seeking behavior through further shopping and buying, thus closing a cycle of self-reinforced behaviors. Both group of researchers developed their own scales based on these roughly equivalent approaches to CBD. One study pointed to the complementary nature of these scales, reflecting the interrelated aspects of both models. Although subtle, the difference between shopping (perusing showcases and malls and analyzing objects in display) and actual buying (the exchange of money for the acquisition of a desired object) seems relevant. Indeed, it appears that Valence's approach has a better focus over shopping behavior and its effect over affect regulation, while Faber and O'Guinn's perspective seems to better capture the extremes of uncontrolled buying, associated behaviors, and consequences. Thus, their scale may be better suited for the assessment of clinical samples. In both cases, the models suggest that CBD cannot be characterized solely by impulsive purchasing, which for that purpose has to be combined with attempts at emotional self-regulation by shopping and buying.

In 1994, McElroy and colleagues proposed the following diagnostic criteria for CBD, emphasizing the inability to resist the impulse to buy:

(A) Maladaptive preoccupation with buying or shopping, or maladaptive buying or shopping impulses or behavior, as indicated by at least one of the following:
   1. Frequent preoccupation with buying or impulses to buy that is/are experienced as irresistible, intrusive, and/or senseless.
   2. Frequent buying of more than can be afforded, frequent buying items that are not needed or shopping for longer periods of time than intended.

(B) The buying preoccupations, impulses, or behaviors cause marked distress, are time-consuming, significantly interfere with social or occupational functioning, or result in financial problems (e.g., indebtedness or bankruptcy).

(C) The excessive buying or shopping behavior does not occur exclusively during periods of hypomania or mania.

These criteria are currently the most employed, despite the scarcity of studies endorsing their validity and reliability. The lack of official and specific diagnostic criteria for CBD is an additional factor contributing to the disorder's permanence in a residual diagnostic category in the section for Impulse Control Disorders Not Otherwise Specified (APA 2000).

It is important to differentiate normal from uncontrolled buying. Essentially, the distinction is not based on the quantity of money spent in relation to the income level, but on a subjective feeling of irrepressible urges to buy, the experience of being out of control while buying (e.g., feeling as if one's behavior was led by an external force), the extent of worry, the degree of distress suffered by the individual, and the appearance of adverse and negative consequences. At any moment of their lives, people may experience an occasional shopping binge, particularly in special occasions such as birthdays or holidays. However, isolated episodes of unrestrained buying should not be confused with CBD's impulsive, harmful, and recurrent purchasing.

Several researchers have developed instruments for the investigation and diagnosis of CBD or for severity assessment. The Minnesota Impulsive Disorders Interview (MIDI), developed by Christenson et al. (1994), is a semi-structured interview that evaluates the presence of CBD, kleptomania, trichotillomania, intermittent explosive disorder, compulsive sexual behavior, pathological gambling, and compulsive exercise. Grant et al. (2005) report that based on McElroy's criteria for CBD, the MIDI presented a sensibility of 100 % and specificity of 96 %.

Faber and O'Guinn's (1992) previously mentioned scale, the CBS, is a seven-item self-report one-dimension scale with high internal consistency (Cronbach's alpha = 0.95) that seems to reliably distinguish normal from compulsive buyers, with estimated sensitivity of almost 90 % and specificity of 85 %.

Monahan and colleagues (1996) adapted the Yale-Brown Obsessive-Compulsive Scale (YBOCS – 1989) to measure the severity of CBD. The YBOCS – Shopping Version (YBOCS-SV) evaluates cognitions and behaviors associated with CBD. It has been mostly used to assess the effects of treatment in clinical trials. The mean pretreatment score for CBD patients was 21 (range 18–25), which was grossly larger than the mean score of 4 (range 1–7) for healthy controls. Unlike the other scales that base their approach on the impulse control disorder framework, due to its original source, the YBOCS-SV is able to tap into the compulsive aspects of CBD.

In that sense, the Richmond Compulsive Buying Scale is unique in its attempt to combine both impulsive and compulsive aspects of CBD. The authors also tried to address another conceptual limitation due to a tautological flaw in the definition of psychiatric disorders by which a behavioral syndrome constitutes a disorder because it implies negative consequences and the reason why it causes negative consequences is because it is a disorder. Thus, Richmond's CBS focuses on behavioral aspects of buying rather than shopping and purposefully avoids tapping into negative consequences. It has convergent validity with Faber and O'Guinn's CBS and its six-item simple structure makes it feasible for population surveys (Ridgway et al. 2008).

Other scales have been developed by various groups, but have not seen ample use; for a thorough overview of the available CBD-related scales and their psychometric properties, usage, and references, the reader may access the address http://www.knowmo.ca/capacity/addictionmeasures/addictionmeasureslist.aspx?BlogTagID=e9193db3-b04d-4b3b-aecb-fdd7c507add8 at the Know Mo website, which stands for Alberta's hub for mobilizing knowledge about addictions and mental health.

96.2.3 Psychiatric Comorbidity and Relationship with Other Mental Disorders

The association of CBD with other psychiatric disorders is the rule rather than the exception, with comorbidity most often seen with mood, anxiety, substance use, eating, and other impulse control disorders (Christenson et al. 1994; McElroy et al. 1994; Schlosser et al. 1994; Black et al. 1998, 2000; Ninan et al. 2000; Black 2001; Mitchell et al. 2006; Mueller et al. 2009).

A bicentric study analyzed data from US and Germany treatment centers and found that approximately half of the sample had at least one current psychiatric comorbidity, mainly an anxiety disorder, and that 90 % fulfilled criteria for at least one Axis I diagnosis during the lifetime. The main diagnoses were mood disorder (74 %), anxiety disorder (57 %), and impulse control disorder (21 %) of which intermittent explosive disorder was most common (Mueller et al. 2010).

It is not uncommon for CBD patients to build up collections of similar items varying one single aspect, e.g., color, size, or design, to zealously stock and hoard them, not allowing other people to interfere with them. For this reason, a relationship with obsessive-compulsive disorder (OCD) has been speculated. However, only one study has found a relevant association, reporting that seven (35 %) out of 20 patients consecutively admitted for CBD treatment had a lifetime diagnosis of OCD (McElroy et al. 1994). Conversely, CBD has been described as a frequent comorbidity among OCD and eating disorder patients (Fernández-Aranda et al. 2008, 2006), with a suggestion that in OCD such an association represents a more impulsive subtype (approximately 10 % of the OCD patients – Hantouche et al. 1997; du Toit et al. 2001). The hoarding behavior seems to be the psychopathological link between the two disorders and for both of them a marker of a compulsive trait and severity (Frosts et al. 2009). For CBD, severity goes hand in hand with psychiatric comorbidity; thus, the presence of hoarding behavior is associated with mood, anxiety, and eating disorders (Kyrois et al. 2004).

On the other hand, the frequent comorbidity with depression and unrestrained expenditure have been pointed as evidences of a link between CBD and bipolar disorder and the former as a member of the so-called bipolar spectrum of disorders (Akiskal et al. 2000). In trying to clarify if CBD should be regarded as a sub-syndromal bipolar disorder, an OCD-related disorder, or a condition apart from the spectrums of both disorders, Filomensky and colleagues (2012) investigated 80 individuals undergoing outpatient treatment for either bipolar disorder, OCD, or CBD regarding impulsivity, obsessive-compulsive traits, hoarding, and mood spectrum of symptoms. Compared to the other two conditions, CBD patients scored significantly higher on all impulsivity measures and especially on the non-planning subdimension. In the hoarding spectrum, they scored higher for the acquisition subdimension, but not for difficulty discarding or cluttering subdimensions. Manic symptoms were distinctive of BD patients, while elevated scores on the contamination/washing and checking dimensions differentiated OCD patients. A discriminant model built with these variables correctly classified

79 % of the CBD outpatients, 71 % of the bipolar patients, and 77 % of the OCD. The authors concluded that given the high impulsivity involved and the intense acquisition desire, CBD, like pathological gambling, was closer to an impulse control disorder resembling a behavioral addiction. These findings establish an interesting parallel with a previous study that described two independent factors for the occurrence of a compulsive episode: an urgency/desire to buy and loss of control over buying (Nataraajan and Goff 1991).

Regarding the acquisition desire, other authors have described that in resisting a purchase CBD patients feel like they are wasting a "must have" opportunity, correlating this feeling to excessive materialism (Kyrios et al. 2004; Mueller et al. 2011) and underscoring the semblance with impulse control disorders. The relationship of CBD with other impulse control disorders needs to be further investigated. There are evidences of comorbidity with psychogenic excoriation, compulsive eating, and other compulsive/addictive behaviors (Christenson et al. 1994; Schlosser et al. 1994; Lejoyeux et al. 1997; Mueller et al. 2009, 2011).

With regard to personality disorders, very few studies have investigated Axis II disorders in the population of compulsive buyers. The two most important studies revealed that the disorders most observed were from clusters B and C: borderline, obsessive-compulsive, and avoidant personality disorders. The first study demonstrated that around 60 % ($N = 46$) of the compulsive buyer patients presented with at least one of the personality disorders mentioned above (Schlosser et al. 1994), and the second around 73 % ($N = 30$) (Mueller et al. 2009).

96.2.4 Clinical Manifestations and Subtypes of Compulsive Buyers

Black (2007) described four phases to characterize an episode of compulsive buying: the first is the anticipation, in which the compulsive buyer experiences thoughts, anxiety, or worry regarding the acquisition of a particular object or simply the act of buying itself. The second phase is the preparation, in which the person prepares him- or herself to go shopping, including researching the desired object, deciding on the clothes that will be worn while shopping, deciding when to go, where to go, and how to pay. This phase can be rather shortened depending on the degree of emotional instability. Negative emotions such as anger, anxiety, boredom, and self-criticism have been related to compulsive episodes of buying (Miltenberger et al. 2003). When pressured by an intense negative affective state, the CBD patient feels the need to quickly perform a purchase, regardless of the nature of the purchased object, or they may feel a need to purchase an object to which they are particularly fixated, e.g., a nail polish flask, a CD of their favorite artist, etc. The purchase, per se, is the third phase, in which compulsive buyers report the emotional experience of the act of buying and the ecstasy. Finally, the fourth phase is the consummation of buying, accompanied by immediate relief of the negative affective, but often shortly followed by self-deception and unpleasant feelings such as guilt or regret. Several authors underscore this narrow association between buying and the need to regulate negative affective sates.

Compulsive buyers divert their attention away from these internal negative emotions and onto external stimuli, which generates an increase in risky compulsive behaviors (Faber and Vohs 2004; Baumeister 1991; Claes et al. 2010; Mueller et al. 2011).

In the cognitive sphere, compulsive buying episodes have been associated with means of identity building, "all or nothing" attitudes toward money, hindsight appraisal of purchasing, and gift buying as a way to garner affection and avoid embarrassment (Mitchell et al. 2006; Filomensky and Tavares 2009). Dittmar and Drury (2000) propose that self-image image building is more related to women than men.

It is common for these episodes to occur in a solitary manner, routinely or in the form of purchasing binges. Sometimes to lessen the guilt, compulsive buyers will also buy for their partners, family members, or friends. When buying for themselves, they often – though not necessarily – hide the objects in closets, drawers, or the car trunk. Many of such purchases may never be used. There is no pattern to stores or commercial places in which these episodes of excessive spending occur; however, buyers do have their "favorite" shopping places, catalogues, and online sites. A study that evaluated excessive Internet use among compulsive and non-compulsive buyers concluded that buying through the Internet is more common among compulsive buyers. The same applies for purchases made through the television (Mueller et al. 2011).

DeSarbo and Edwards (1996) described two subtypes of compulsive buyers: one group in which the principal trigger of a compulsive episode was the materialism and desire for objects with a tendency to be more impulsive and the second group in which the compulsive episode was more motivated by internal emotions such as low self-esteem and little control over the desire to buy. This second group presented with a higher propensity to develop depression. Likewise, another study pointed to two distinct groups among compulsive buyers: one in which the motivation for the purchase was guided by positive reinforcement related to pleasant aspects of the purchase and the other in which the purchase occurred as a result of emotional suffering associated with financial problems, interpersonal relationships, and emotional questions, revealing a group with significantly higher levels of debt (Thornhill et al. 2012).

Therefore, like previously described for pathological gambling, CBD seems to encompass a double nature, an impulsive side related to purchase cravings and lack of planning and a compulsive side characterized by the avoidance of negative emotions and attempts to control one's affective state, both combined lead to loss of control over buying. The determination of the subtype depends upon which side prevails (Tavares and Gentil 2007).

96.2.5 Social-Cultural Issues

Social-cultural factors alone cannot be blamed for CBD occurrence; however, it is important to consider their influence. The easy access to growing amounts of credit

is a worldwide phenomenon, and in the last decades there have been a shift in advertising strategies from focusing on the qualities of the purchase to how good purchasing makes you feel. This is especially true for countries in which the economy is consumer based (Black 2007).

An almost universal selling strategy is to anticipate the pleasure of the acquisition through credit card shopping or other option and to delay the "pain" of payment, to which impulsive individuals may be particularly vulnerable. Indeed, several measures of compulsive shopping have a strong correlation with credit card use and credit card minimum payment (Faber and O'Guinn 1992; Ridgway et al. 2008). The credit card has become a cultural icon, going beyond a mere form of modern "plastic cash," something particularly noticeable in developing economies and most appealing to vulnerable women as a promise of more autonomy in societies largely dominated by men (Hanley and Wilhelm 1992).

96.2.6 Neurobiology, Genetics, and Risk Factors

Family studies of compulsive buyers show a heavy concentration of mood, anxiety and eating disorders, substance use, and other impulse disorders, including CBD itself. Evidence also exists showing that traumatic childhood events such as sexual abuse are factors that predispose the development of CBD (Black 2007; Black et al. 1998; McElroy et al. 1994). A study of 370 gynecology patients investigated the relationship between five traumatic experiences in childhood (before the age of 12) and CBD. The results indicated that childhood trauma is associated with compulsive buying behavior, particularly when the trauma was emotional in nature or involved witnessing violence (Sansone et al. 2013). However, there are no data on how childhood trauma and early adversities can build a specific vulnerability to consuming behavior or if it would be an unspecific vulnerability factor for various psychiatric syndromes.

There are few neurobiological studies of CBD, and most are concentrated on the loss of regulation over the serotonergic, dopaminergic, and opioid neurotransmission. Due to the diagnostic doubt that haunts CBD, researchers who note similarities between CBD and OCD use selective serotonin reuptake inhibitors (SSRIs), as it is a common and effective treatment for OCD, but so far its efficacy in CBD and the role of serotonin transmission in CBD remain undetermined (Black et al. 1997; Koran et al. 2003).

Potenza (2001) proposes that compulsive purchases, pathological gambling, and other self-indulgent behaviors are related to factors involving low dopaminergic activity, the so-called brain reward deficiency syndrome (BRDS). Thus, the preferred biological tools to intervene in CBD would be those directly or indirectly modulating dopamine transmission, through opioid and glutamate modulation, in the brain reward system. Few reports have suggested the benefits of treating CBD with the opioid antagonist naltrexone, raising speculations about the role of β-endorphin and opioid receptors in CBD (Grant 2003). A preliminary study with memantine, an antagonist of the N-methyl-D-aspartate receptor, resulted in reduced

glutamate excitability, in addition to improving the compulsive buying behavior of patients with CBD (Grant et al. 2012). In any case, proposals regarding neurotransmission remain up to now speculative, with no studies so far having directly examined the neurotransmitters involved in CBD, through either plasma levels or cerebrospinal fluid.

Comings et al. (1997) found a significant correlation between the polymorphism of the D1 receptor gene and Tourette's syndrome, pathological gambling, alcohol abuse, and CBD, corroborating the BRDS hypothesis. Another study investigating the polymorphism of the promoter region of the serotonin transporter gene did not find any association with CBD. However, it is important to note that this study involved a small sample and studied only the association with alleles of small effect (Devor et al. 1999). A recent study carried out by De Neve and Fowler (2010) identified an association between the polymorphism of the MAO-A gene and a higher probability of credit card debt. The MAO-A is implicated in the metabolism of serotonin and has one or both of the variant alleles of low efficacy associated with higher probability of addiction and impulsivity.

So far, no neuroimaging studies with CBD diagnosed individuals have been conducted. Nevertheless, one study using functional magnetic resonance imaging in a nonclinical sample observed activation of the nucleus accumbens when the subjects anticipated an advantageous purchase. This is the same structure over stimulated by drug addictions, which confirms the involvement of brain reward system in buying behavior. Conversely, disadvantageous offers, i.e., excessive prices, activated the insula and deactivated the mesial prefrontal cortex, indicating the involvement of different circuitries in the decision-making process related to purchasing. Interestingly, other studies have associated the insula activity with the experience of physical pain and its emotional component (Knutson et al. 2007).

96.2.7 Treatment

96.2.7.1 Psychotherapy

Over the past 5 years, studies regarding the treatment of CBD established important advances, as what existed were previous case reports aligned to the theoretical orientation of the authors. Still, controlled studies evaluating treatment efficacy for CBD, independent of therapeutic modality, remain scarce (Kellett and Bolton 2009; Benson and Gengler 2004; Mitchell et al. 2006; Steketee and Frost 2003).

Cognitive-behavioral models remain as the most tested and studied treatment programs. The first studies were by Lejoyeux et al. (1996) and Bernik et al. (1996), both of which suggested that cue exposure and response prevention may be useful in the treatment. Bernik and colleagues (1996) reported on two cases treated with clomipramine for panic attacks, who also presented with CBD. The medication did not improve compulsive buying behavior; however, both responded well to 3–4 weeks of buying cue exposure and response prevention, although no posttreatment information was provided.

One of the first to use the cognitive behavioral therapy group were Burgard and Mitchell (2000). A pilot study carried out by Mitchell et al. (2006) involved 28 patients with CBD diagnoses for the treatment with a cognitive-behavioral model and 11 controls on the waiting list. At the end of 12 weeks, the results showed significant advantages of cognitive-behavioral therapy, with subjects outperforming the waiting list controls in terms of the number of compulsive buying episodes and time spent buying. This improvement was maintained over the following 6 months. In 2008, Mueller et al., inspired by the Mitchell et al. (2006) study, treated 31 compulsive buyers with a 12-week cognitive-behavioral intervention and compared them with 29 control patients on the waiting list. The treatment sessions specifically dealt with problems related to compulsive buying, restructuring of negative thoughts and emotions regarding buying, control over buying behavior, and problem-solving skills. Throughout the next 6 months, the patients continued to present with improvements when compared with the control group.

Imaginary desensitization was also used to treat a female compulsive buyer with a treatment package that also included motivational interviewing, financial planning, leisure, and cognitive restructuring. The final evaluation was positive, showing a reduction in compulsive episodes (Donahue et al. 2011). Another uncontrolled study reported on a cognitive-behavioral group intervention with an emphasis on cognitive restructuring. Specific sessions were devised to deal with the most common cognitive distortions related to buying such as buying as a way of coping with emotions and building an identity and "all or nothing" type of thinking. The nine patients who participated all reported improvement of both cognitions and behaviors related to CBD (Filomensky and Tavares 2009).

96.2.7.2 Psychopharmacology

Similar to psychotherapeutic treatments, controlled clinical trials for CBD are scarce. Lejoyeux et al. (1995) suggest that depressive compulsive buyers have an increased chance of improving their compulsiveness when treated with antidepressants than compulsive buyers without depression. A clinical trial with ten patients evaluated the use of fluoxetine in compulsive buyers over 9 weeks. Nine of the ten patients showed improvement, suggesting that it is not necessary for patients to be depressed in order to benefit from antidepressants (Black et al. 1997).

Two randomized controlled clinical trials with fluoxetine were carried out soon after. The first treated 37 compulsive buyers over the course of 12 weeks and did not find a difference between fluoxetine and placebo (Ninan et al. 2000). The second studied a sample of 23 CBD inpatients without depression (Black et al. 2000). The participants were randomly distributed to fluoxetine ($n = 12$) or placebo ($n = 11$). At the end of 9 weeks and applying the Scale of Global Clinical Improvement, 50 % of the patients in the fluoxetine group and 64 % of those in the placebo group were classified as showing "great" or "very great" improvement. The positive response of the placebo group points to the need to undertake more randomly controlled trials with longer follow-up periods (Christenson et al. 1994; Black 2001).

A clinical trial with citalopram showed favorable results in the double-blind discontinuation study carried out by Koran et al. (2003). Twenty-four patients with

CBD were selected, and after 6 weeks of treatment, 17 patients presented with a significant reduction in spending and purchases and an improvement in global functioning. Then, these patients were randomly assigned to either citalopram or placebo maintenance for 9 more weeks. The seven patients that took citalopram did not relapse, while five of the eight patients who took the placebo relapsed. After 1 year, 73 % of the seven patients who took medication remained in remission from compulsive symptoms even after having interrupted medication. The authors suggested that citalopram treatment might have modified the natural course of the disorder. On the other hand, another study with a similar design using escitalopram found no significant effect (Koran et al. 2007).

Grant (2003) reported on the successful treatment of three patients with naltrexone, and recently memantine was tested in nine CBD patients with encouraging results (Grant et al. 2012).

96.2.8 Self-Help/Community Resources

Other treatments have been elaborated as complementary to those more traditional ones that could be useful. These include self-help books about CBD for individual clarification or group discussion. The Debtors Anonymous group, which was created with the same perspective of Alcoholics Anonymous, is a self-help group coordinated by laymen who have the same difficulties and who provide support and encouragement for those with substantial debt. Simplicity Circles, which exist in some American cities, is a group of volunteers who encourage people to adopt a simple lifestyle, to resist consumerism appeal, and to abandon CBD. Finally, couple and financial counseling may be beneficial as relationships and financial status of the family become stranded because of chronic CBD (Black 2007).

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Sexual Addiction

97

Meyen Hertzsprung and Stephen Amadala

Contents

Abstract

Excessive sexual behavior or hypersexuality has been documented clinically in the western world since the eighteenth century. Individuals affected by such behavior have symptoms akin to those with substance dependence. The concept of sex addiction share features with substance dependence such as distress due to negative consequences of compulsive sexual behavior and impulsive sexual behavior. This chapter reviews the evidence for the concept of sex addiction and discusses the assessment, etiology, neurobiology, prevalence, comorbidity, and treatment approaches.

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Sex addiction • Compulsive sexual behaviour • Hypersexuality

97.1 Introduction

Phenomena of excessive sexual behavior have been documented clinically in the western world since the eighteenth century. Descriptions of "excessive and maladaptive" sexual behavior (Kafka 2010) served as precursors to what became known in the twentieth century as "Don Juanism," characterized by excessive sexual appetite and protracted promiscuity, and became codified in the International Classification of Diseases (ICD 2007) as excessive sexual drive (F52.7).

In the 1970s, 12-step recovery groups addressing "out-of-control" sexual behavior began to arise independently and spontaneously throughout a number of cities in the United States. Most of these groups were formed by members of Alcoholics Anonymous (AA) groups and followed 12-step format and principles. These groups placed excessive sexual appetites/behavior within the rubric of "addiction" (Irvine 1995). However, it was the publication of Patrick Carnes' *Out of the Shadows* in 1983 that signaled the emergence of "sex addiction" into the world of science and media, and the first inpatient treatment programs for "sex addicts" were introduced.

"Sex addiction" was a grassroots term that seemed to capture the experience of those struggling with seemingly "out-of-control" sexual behavior and emphasized commonalities between AA members' experience with sex and their experience with alcohol. Although the term was controversial, by the late 1980s, extensive media coverage popularized the idea of sex addiction, and since then it seems like every few years various celebrities would admit to sex addiction and enter treatment. Still, controversy remains over whether or not sex addiction exists, with concomitant impairments in cognition, impulse control, attachment, intimacy, and mood, or has simply been invoked as a convenient excuse for an individual's sexual indiscretions (Karim and Chaudhri 2012).

In the 1990s widespread access to the Internet lent a new dimension to sex addiction. Suddenly "an essentially unlimited range of sexually explicit texts, still and moving images, and audio materials" were available for immediate and secret consumption (Fisher and Barak 2001). As if the task of definition and classification were not complicated enough, technology further added to the complexity of what was described as compulsive sexual behavior. The Internet has become the arena of ever-varied forms of cybersex. Since the 1990s, "sex" has been the most widely used search term on the World Wide Web (Hertlein and Piercy 2008), and about a third of all data traffic on the Internet involves pornography (Anthony 2012).

The use of the Internet itself has become the focus of considerable attention in the literature, as it can also become problematic and excessive. Hertlein and Piercy (2008) noted that high levels of general Internet use accounts for lower levels of family communications and social interactions and higher levels of depression and

loneliness within families. It can be tricky to differentiate between general Internet use and online sexual behavior, however. For example, Young (2009) identified three subtypes of "Internet addiction": (1) excessive gaming, (2) online sexual preoccupation, and (3) email/text messaging. It is easy to see that all three subtypes (and not just the second) can have a sexual component to them. Role-playing games often involve sexual encounters between fantasy avatars; and email/text messaging can be and has been the means for sharing sexual preoccupations.

Thus, online sexual behavior could be a subset of Internet addiction or could be a technological variant of sex addiction (Ross et al. 2012); both of these also need to be distinguished from an online "affair," or Internet infidelity (Jones and Hertlein 2012). Indeed, as technology advances, the task of delineating boundaries around "sex addiction" becomes more complicated. "Cybersex" no longer denotes just viewing pornographic texts or images; there is now a significant interactive component to cybersex that defies straightforward classification. Dryer and Lijtmaer (2007) take a psychodynamic approach to the meanings of cybersexual encounters, noting that these interactive components (instant messaging, texting) add to these encounters a unique kind of "techno-intimacy." Their paper highlights the specific dynamics of this "twilight zone" of techno-intimacy, which in many ways constitutes a simultaneous virtual and real sexual "relationship," wherein the individual is able to be both "there" and "not there." Doubtless this twilight zone would require further exploration, as these virtual/real relationships also become more and more portable with the advent of smart phones.

Also in the early to mid-2000s, more attention was being paid to the effects of sex addiction on couples and families. The term "codependence," widely used with respect to partners of alcohol and drug dependents, came under criticism as a term that pathologized normal reactions to extreme situations (van Wormer 1990). Rather, partners are invited into treatment as those who have suffered a traumatic experience with the discovery or disclosure of compulsive sexual behaviors (e.g., Black and Tripodi 2012). In addition, an entire literature on managing disclosures has developed (e.g., Schneider and Levinson 2006).

The purported diagnosis of "sex addiction" was controversial from the beginning, in terms of both its existence and nosology. There have been arguments and evidence for and against conceptualizing a particular constellation of behaviors as an addiction, an impulse control disorder, an impulsive-compulsive behavior, or as symptoms of an underlying Axis I disorder; and the search for neurobiological substrates underlying each argument continues. As already noted, the emergence of the Internet has complicated matters further. Nevertheless, there seems to be consensus regarding the clinical presentation of such individuals, varied though they may be (Gold and Heffner 1998; Kafka 2010). As already noted, sex addiction (also known as compulsive sexual behavior, sexual impulsivity, or hypersexual disorder) is a controversial topic in both media and science (TIME 2011). Controversy is bound to occur when any class of behaviors, including sexual behaviors that are considered "normal," are medically pathologized (Money 1994).

Sexuality depends on many factors, including relationship variables, societal values, cultural norms, and ethnic and cultural beliefs; these need consideration

when discussing hypersexuality (Kaplan and Krueger 2010). The group of individuals easiest to diagnose with a form of sexual addiction are those (primarily men) who meet criteria for paraphilia disorders (Kafka 1994). This is due to societal and legal sanctions that consign these individuals to the legal system for punishment or medical system for treatment. Outside the paraphilias, sexual addiction typically presents with specific behaviors that are socially sanctioned but often cause significant distress with concomitant problems such as substance abuse or mental disorders (Schneider and Irons 2001; Carnes 1991).

There is a challenge in defining abnormal and pathological practices. Carnes and Wilson (2002) proposed that sexually addictive behaviors include compulsive masturbation, affairs and use of prostitutes, pornography, cybersex, voyeurism, exhibitionism, sexual harassment, and sexual offending. They divided the behaviors into three levels, in ascending order of potential serious concern. Level I behaviors, by far the most controversial category, include behaviors that are commonplace and widely accepted as being normal and unproblematic (masturbation, using pornography, visiting strip shows, prostitution). Carnes noted that these may have "devastating" consequences if compulsive or involving the "victimization of others." Level II behaviors "are sufficiently intrusive to warrant stiff sanctions." Such behaviors all involve some form of victimization and include exhibitionism, voyeurism, and indecent phone calls. Level III behaviors include the most serious forms of sexual victimization (child molestation, incest, rape, and violence). Goodman (1992), employing a contemporary definition of substance addiction (DSM IV Criteria), proposed to replace the word substance with sexual behavior and formulated criteria to describe sexual addiction disorder. Kafka (2010) proposed "hypersexual disorder" for consideration in the sexual disorders section for DSM V. It is conceptualized primarily as a nonparaphilic sexual desire disorder with an impulsivity component (Kafka 2010). The proposed diagnostic criteria for hypersexual disorder (American Psychiatric Association DSM V Development 2010) include recurrent and intense sexual fantasies, sexual urges, or sexual behaviors over a period of at least 6 months. This is in association with three or more of the five criteria related to repetitive sexual fantasies, urges, or behaviors and determined by the following: time consumed interfering with other important goals, activities, and obligations; engagement in response to dysphoric mood states or in response to stressful life events; unsuccessful efforts to control or significantly reduce these fantasies, urges, or behaviors; and disregard for the risk for physical or emotional harm to self or others.

These fantasies, urges, or behaviors are associated with clinically significant personal distress or impairment in social, occupational, or other important areas of functioning, and are not due to the direct physiological effect of a drug of abuse or a medication.

Kafka formulates "hypersexual disorder" as "a sexual desire disorder" characterized by an increased frequency and intensity of sexually motivated fantasies, arousal, urges, and enacted behavior in association with an impulsivity component – a maladaptive behavioral response with adverse consequences. "Hypersexual disorder" is associated with increased time engaging in sexual

fantasies and behaviors (sexual preoccupation/sexual "obsession") and a significant degree of volitional impairment or "loss of control" characterized as disinhibition, impulsivity, compulsivity, or behavioral addiction (Kafka 2010). Kafka avoided referring to "hypersexual disorder" as an addiction; however, his criteria are quite similar to those proposed by Goodman. The major difference between the two sets of criteria is the absence in "hypersexual disorder" of symptoms crucial to the addictive disorders concept, such as tolerance symptoms, and relief resulting from sexual behavior.

97.1.1 Relationship with Paraphilias

Paraphilias are characterized by intense, repetitive, deviant, sexually arousing fantasies and sexual urges and behaviors lasting at least 6 months and marked by personal distress or indications of significant psychosocial impairment related to sexual behavior. In contrast hypersexual behavior is characterized by excessive repetitive expression of culturally adapted normophilic sexual behaviors. As with other disorders, these disorders are not deemed mutually exclusive.

97.2 Management of Sexual Addiction

97.2.1 Assessment

Treatment begins with a comprehensive assessment. This includes current presentation and history of the "sexual addiction." The clinician must establish what precipitated the visit: what are the behaviors of concern, at what frequency do they occur, and under what circumstances do they occur? What is the sex and age of partners involved? What is the timeline of the behavior? When were the behaviors worst and what were the factors that contributed to their exacerbation? What has helped reduce the behaviors or the distress? Finally, what has been the impact of the behavior on various aspects of functioning? Particularly important would be a review of current relationships and the impact of the behaviors on family and friends.

With regard to history, the clinician must assess any sexual or physical abuse, or neglect, as well as review the medical history, including any treatments for sexually transmitted illnesses. The clinician must inquire into other addictive behaviors and their relationship with sexually acting out behaviors. In addition, assessing for any legal involvement, past and present, would be important, as well as mental health function and any comorbid psychiatric disorders.

A number of screening and assessment instruments are available, including the Sex Addiction Screening Test (SAST); the PATHOS, a short screening interview analogous to the CAGE for alcohol use; the Compulsive Sex Behavior Inventory; and the Sexual Compulsivity Scale. Carnes (1989, 1991) developed the SAST, a 25-item dichotomously answered self-administered questionnaire. The SAST has

demonstrated a single factor with high internal consistency in a sample of 191 sexually addicted, in comparison with 67 nonaddicted males. A cutoff score of 13 (out of 25) is likely indicating the presence of a sexual addiction in heterosexual males. The SAST was revised in 2010 (SAST-R) (Carnes et al. 2010).

The PATHOS (derived from the SAST and SAST-R) has been developed as a brief screening instrument to assist clinicians with identification of individuals who may have sex addiction (Carnes et al. 2012). A score of 3 out of 6 indicates further assessment for sex addiction.

PATHOS Questionnaire items are as follows:

1. Do you often find yourself preoccupied with sexual thoughts? (**P**reoccupied)
2. Do you hide some of your sexual behavior from others? (**A**shamed)
3. Have you ever sought help for sexual behavior you did not like? (**T**reatment)
4. Has anyone been hurt emotionally because of your sexual behavior? (**H**urt Others)
5. Do you feel controlled by your sexual desire? (**O**ut of Control)
6. When you have sex do you feel depressed afterwards? (**S**ad)

97.2.2 Etiology and Neurobiology

We do not have quality evidence supporting the etiology of sexual addiction. Most of the literature about etiological mechanisms is based on theory: endocrine dysfunction, incomplete monoamine hypothesis, developmental processes and a courtship disorder, social learning theory, and psychodynamic theories. Little is known about the brain pathways that regulate sexual behavior and cognition. Dopamine, serotonin, and androgenic hormones appear to play a critical role (Kafka 2003). Functional imaging with PET and MRI has corroborated that the amygdala, mesencephalic tegmentum, and septal nuclei are activated during sexual response (Arnow et al. 2002). PET scans of healthy volunteers during orgasm and ejaculation showed strong activation of dopaminergic mesodiencephalic junction and ventral tegmental area; the latter region of the brain is also activated with the "rush" experienced by heroin addicts (Park et al. 2001).

Neurobiological correlates of addiction start with the brain reward circuitry: specifically, the mesolimbic reward system (Di Ciara 1998), a region significant for understanding the origins of how addictive behaviors emerge. There is a paucity of literature on brain imaging during conventional or pathological sexual functioning. Reward circuits such as the dopaminergic and endogenous opiates systems have been implicated in the process of sexual behavior in much the same way as substance use (Goodman 2008). The role of the reward system in these disorders is derived from research into Parkinson's disease, whereby treatment with dopamine agonists leads to vulnerability to impulse control disorders such as pathological gambling, hypersexuality, compulsive shopping, and compulsive eating (Vilas 2012). Addiction has usually been defined as dependence on a drug that can "hijack" the reward system. Any stimuli (drug or behavior) that transform the

basic drive required for survival (like feeding, thirst, reproduction) into actions of craving/seeking behaviors or repetitive out-of-control behaviors may make it plausible that addiction can occur even in the absence of drug taking (Karim and Chaudhri 2012). Thus, behavioral addictions may share many of the same pathways associated with chemical dependence. Hence, the theory that "if one can alter neurocircuitry with illicit drugs and pharmacology, then one can alter it with behavior as well" (Holden 2001).

97.2.3 Prevalence

Kafka (1997) attempted to quantify sexually compulsive behavior and distinguish between socially conforming sexual behaviors and behaviors that are nonsocially conforming. They define "hypersexual desire" in men as the persistence of seven or more orgasms per week for a minimum duration of 6 months or more after age 15 (Kafka 1997). This definition characterizes 3–8 % of responses in nationally representative surveys of male sexual behavior in the United States (Kafka 1997, 2003; Black 2000) and Sweden (Langstrom 2006). The definition applies to males and may not be applicable to females, as fewer women engage in high rates of sexual behavior. In one national survey of women, 24.1 % reported sexual intercourse several times a week but only 1.1 % daily; 4.5 % reported masturbation several times a week and 1 % reported daily masturbation. There are no evidence-based estimates of the prevalence of sex addiction, nor reports of the incidence of the disorder.

97.2.4 Comorbidity

One of the consistent findings of studies of those with sexual compulsion was that the great majority have lifetime comorbid mood, anxiety, psychoactive substance use, and/or other impulse disorder diagnoses. ADHD (inattentive subtype) was identified as a co-occurring psychiatric diagnosis in sexual addicts (Blankenship and Laseer 2004). There is a high correlation between sex addiction and substance use disorders, up to 80 % in some studies. This tends to complicate the task of diagnosis and treatment.

With regard to Axis II comorbidity, Raymond et al. (2003) found that the most commonly co-occurring personality issues are Cluster C personality disorders (39 %), followed by Cluster B personality disorders (23 %). Reid et al. (2012) found that men with compulsive sexual behavior exhibited higher levels of emotional dysregulation, stress vulnerability, and interpersonal sensitivity; these characteristics generalized to hypersexual women. They concluded that personality traits associated with emotional problems, difficulties coping with stress, and interpersonal sensitivity may constitute a precipitating or perpetuating risk factor in the onset or maintenance of hypersexual behavior in adult men and women and

that treatment interventions targeting affect regulation, stress coping, interpersonal coping, interpersonal sensitivity, impulsivity, and manipulative tendencies are warranted for both hypersexual men and women.

Neuropsychiatric illness (Vilas 2001) may induce acute changes in sexual behavior; similarly, medications, typically dopaminergic agonists (Kafka 2003), may also contribute to hypersexual behavior. In these circumstances the hypersexual behaviors tend to be a mixture of normophilic and paraphilic-like sexual behaviors (e.g., inappropriate touching and exposing oneself, but not to strangers).

97.2.5 Treatment Approaches

97.2.5.1 Psychosocial Approaches

Patrick Carnes, whose autobiographical book *Out of the Shadows* (1983) brought sex addiction to public attention, has also been instrumental in the development of the most widely published therapeutic approach to compulsive sexual behavior (Herring 2013). Carnes' "task-centered approach," outlined briefly in his introductory workbook *Facing the Shadow* (2005), guides the "recovering addict" through 30 tasks. Each task has a list of "performables" meant to operationalize the task. For example, the first task is to "break through denial" and includes the following performables: make a problem list, make a secret list, make a list of excuses and rationales, complete a consequences inventory (list of consequences in various life areas), make a list of people hurt, find a therapist, find a sponsor, and make full disclosure to therapist and sponsor. Other tasks include such "performables" as reading about sex addiction, generating relapse prevention plans, and participating in a culture of recovery support.

The first seven tasks are meant to guide the "addict" through early sobriety; tasks 8–19 provide longer-term guidance in individual recovery and dovetail with tasks 19–30, which focus on "family recovery." The tasks make the most sense when used in conjunction with involvement with 12-step recovery groups; the "performables" can also serve as a menu of helpful worksheets regardless of therapeutic approach. While many of the "performables" can be directly linked to 12-step recovery (e.g., find a sponsor, complete a powerlessness inventory, share your first step), many others can also be used within the context of relapse prevention and cognitive-behavioral therapy (e.g., identify your relapse scenarios, complete a fire drill plan).

Young (2008) identified three categories of treatment for Internet sex addiction: the first category is Carnes' approach of symptom management and reflection, which initially involves "crisis management" – largely behavioral measures of contingency management, such as moving the computer to a public area and installing safety software – and later addressing underlying issues often related to early childhood development and family of origin. The second category identified involves formulating recovery plans based on "addicts" identifying behaviors which are out of bounds, behaviors which place them at risk, and behaviors that promote health. It must be noted that this work is included in Carnes' tasks as well.

The third category, which Young herself developed, is described as "an integrated recovery approach that combines cognitive-behavioral and insight-oriented therapies," which, based solely on her description, was frankly difficult to distinguish from Carnes' approach.

Carnes was instrumental in the establishment of the Society for the Advancement of Sexual Health (SASH), a nonprofit multidisciplinary organization "dedicated to scholarship, training, and resources for promoting sexual health and overcoming problematic sexual behaviors," such as "sex addiction, hypersexual disorder, out-of-control sexual behavior, sexual impulsivity, sexual abuse" (SASH 2013). SASH holds a conference yearly and recently started offering a certificate for "Advanced Training in Problematic Sexual Behavior."

Carnes also founded the International Institute for Trauma and Addiction Professionals (IITAP), which offers "premier training and cutting-edge educational resources for practitioners who treat people with addictive and compulsive sexual behaviors" and claims that its CSAT (Certified Sex Addiction Therapist) program is "one of the most highly regarded programs of its kind, offering a complete group of training, products and services" (IITAP 2013); Carnes also founded Gentle Path Press, which publishes many of the materials used for training as well as the books recommended through his task-centered approach.

While Stefanie Carnes, clinical psychologist and current president of IITAP, has remarked that the CSAT training is "very strongly research based" (personal communication, 28 March 2011), Rory Reid, research psychologist at the Department of Psychiatry and Biobehavioral Sciences at the University of California, Los Angeles, asserts that "having reference material that is 'research based' is not the same as having a treatment approach that is empirically supported by research" (personal communication, 28 March 2011). Indeed, Reid bemoans the fact that as of early 2011, there were only eight published treatment outcome studies related to the sex addiction population, half of which were single-subject design studies (personal communication, 6 February 2011).

When conceptualized as an addiction, there are many possibilities of extending already established therapies that help with addictive behaviors, such as motivational enhancement therapy, cognitive-behavioral approaches, emotional awareness, and mindfulness-based approaches. Participation in 12-step recovery groups is also routinely recommended in conjunction with psychosocial treatment. However, so far there is a paucity of research evidence to empirically support any one treatment approach for compulsive sexual behavior.

97.2.5.2 Pharmacological Approaches

Pharmacological treatment uses two main categories of medications: specific serotonin reuptake inhibitors (SSRIs) and antiandrogens (Guay 2009). In addition, patients with sexual addiction may present with dysphoric mood symptoms that may warrant antidepressant medications. This usually occurs in the initial phase of abstinence.

There are no randomized control trials for treatment of patients with antidepressants. However, case reports and open-label studies (Kafka 1994; Stein 1992)

indicate that SSRIs may be of use in the treatment of sexual addiction. This is based on the rationale that serotonergic dysfunction may underlie the condition. Madeo (2008) showed in a randomized control trial with citalopram that in healthy adult males, 4 weeks of treatment significantly increased the time to orgasm compared to men on placebo. However, the medications did not dampen sexual desire or penile tumescence measurements, suggesting that SSRIs may have differential effects on dampening libido and sexual function in men who are not depressed or who do not have compulsive sexual behavior. In a randomized control trial, gay and bisexual men with sexual addiction/compulsivity who were treated for 12 weeks with citalopram (20–60 mg a day) reported significant reductions in sexual drive, frequency of masturbation, and viewing of pornography in comparison to those treated with placebo (Weinberg et al. 2006). In summary there is some evidence supporting the use of the SSRI citalopram for sex addiction, especially in gay and bisexual men.

Naltrexone is an opioid antagonist approved for use in treating alcoholism and opioid dependence. It works by dampening dopamine release, thus reducing the euphorigenic effects of fantasizing and tension building which are considered the initial steps in compulsive sexual behaviors. There are no randomized trials of opioid antagonists for sexual addiction. Some open-label trials show that high doses of naltrexone reduced frequency of masturbation, sexual fantasies, and nocturnal emission (Bostwick and Bucci 2008).

Antiandrogen medications currently used for treatment of excessive nonparaphilic sexual behavior are cyproterone acetate (a synthetic steroid similar to progesterone which acts both as a progesterone and an antiandrogen) and medroxyprogesterone acetate. Medroxyprogesterone acetate diminishes libido in men and thus makes it easier to control sexually addictive behavior. The rationale of using hormone therapies in men with sexual addiction is based on eliminating sexual compulsivity and obsessions by stopping the production of testosterone. This approach is usually reserved for treating paraphilias in men that involve sexual offending involving children and violence (Thibaut et al. 2010; Gottesman and Schubert 1993). Antiandrogens diminish sex drive in women; hence, the use of antiandrogens in women to control hypersexuality may be of benefit.

Goodman (1998) has presented a psychotherapeutic stage model integrating pharmacotherapeutic, behavioral, and psychodynamic approaches. In the first stage (initial behavior modulation), individuals who engage in addictive sexual behavior learn how to modulate their behavior through a combination of inner motivation, psychological support, and affect-regulating medication; the second stage (stabilization of behavior and affect) addresses the question of relapse prevention, with a distinction between high- and low-risk forms of sexual behavior. Patients are taught to engage in "healthier" forms of sexual behavior.

97.3 Conclusion

Sex addiction as a concept carries a lot of controversy. In the last two decades, there has been an effort in defining the features of sex addiction. The proposed inclusion

of hypersexual disorder in the DSM V would help in furthering research in this field, provide a reference for clinicians, and help in the recognition and treatment of this disorder (Kafka 2010). There is frequent comorbidity with psychiatric disorders, especially substance dependence, bipolar disorder, and personality disorders. There is a paucity of research about the prevalence and incidence of the disorder. The treatment of the disorder encompasses a variety of treatment approaches including psychotherapeutic models and pharmacotherapeutic interventions (especially for concurrent psychiatric disorders). Twelve-step organizations are an integral part in helping individuals seeking help and recovery (Reid 2007; Carnes 1989).

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The Association Between Binge Eating, Obesity and Addiction

98

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Contents

Abstract

Obesity has become a worldwide pandemic with an estimated annual cost in related illnesses and loss of productivity over $100 billion and rising. Though not recognized as a psychiatric disorder, obesity has been linked to serious physical, psychological, and social consequences. Some forms of obesity are typified by the compulsive consumption of food, difficulty curbing further intake despite negative consequences, a desire to cut back, as well as needing increasing amounts of food to reach satiety, resembling a form of tolerance. These symptoms are remarkably similar to DSM criteria for substance use disorders. Research in both animals and humans has demonstrated food-related changes in the brain itself that are very similar to changes caused by drugs of abuse leading to the hypothesis that some forms of obesity and a related

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contributing behavior, binge eating, may manifest secondary to or along with a "food addiction." This chapter seeks to describe the common elements and possible intersection of binge eating disorder, obesity, and addiction.

98.1 Introduction

This chapter seeks to describe the common elements and possible intersection of binge eating disorder, obesity, and addiction. The Diagnostic and Statistical Manual of Mental Disorders V (DSM-V) currently recognizes Anorexia, bulimia, binge eating disorder (BED), and FED-NEC secondary to the serious impairments and severe negative outcomes associated with these conditions (APA 2013). Unlike eating disorders, obesity is not currently recognized as a psychiatric disorder. However, obesity has been linked to serious physical, psychological, and social consequences. Some forms of obesity are typified by the compulsive consumption of food, difficulty curbing further intake despite negative consequences, a desire to cut back, as well as needing increasing amounts of food to reach satiety, resembling a form of tolerance (Volkow and O'Brien 2007; Taylor et al. 2010). These symptoms are remarkably similar to DSM criteria for substance use disorders. These symptoms are remarkably similar to the DSM-IV criteria for substance abuse and dependence: preoccupation, escalation, tolerance, denial, and a series of medical, psychological, and social consequences that relate directly to continued use (APA 2013; Gold et al. 2009), thereby leading to the hypothesis that some forms of obesity and a related contributing behavior, binge eating, may manifest secondary to or along with a "food addiction."

The concept of food addiction is a highly debated one (Avena et al. 2012b). One argument against the notion that food is addictive is, of course, that everyone eats. How can something that sustains life be considered addictive? It has been proposed, however, that only certain foods be considered addictive, specifically those high in sugars and fats. These "forbidden" foods are typically calorie dense, highly palatable, and the types of foods that people tend to overconsume most (Corwin and Grigson 2009). Studies using animal models have provided a great deal of empirical support for the concept of food addiction. Such studies have found that similar to substance addictions, the consumption of these types of foods increases dopaminergic activity in the brain's mesolimbic reward circuits and leads to increased intake over time, and when animals are deprived of these foods, a history of such consumption can precipitate symptoms of withdrawal (Avena et al. 2008). More recently, tools have been designed to assess food addiction in humans, and studies incorporating such tools are beginning to provide additional evidence of this construct. For example, more than half of obese individuals with binge eating disorder included in one study met the criteria for food addiction (Gearhardt et al. 2012). Using fMRI scanning, individuals with greater food addiction scores have also been shown to have greater activation of motivation-related brain regions when anticipating highly palatable food, similar to drug-addicted individuals when viewing cues associated with a drug (Gearhardt et al. 2011).

Disordered eating, such as that seen in binge eating disorder, bulimia nervosa, and some cases of obesity, poses a number of complications for the medical community. These conditions can be physically compromising and, in some cases, even fatal; however, their etiology is not well characterized. Expert speculations regarding the underlying risk factors for the development of disordered eating include a range of psychological, biological, and societal influences. Given the growing evidence of neurochemical and behavioral similarities between overconsumption of certain foods and substance addiction, and the urgent need to develop effective treatments to combat obesity and overeating, it may be time to consider food addiction as a possible contributing factor to these issues, as well as a target for treatment.

98.2 Feeding and Reward

Feeding behaviors are controlled by more than homeostatic mechanisms. As it has been pointed out, "if feeding were controlled solely by homeostatic mechanisms, most of us would be at our ideal body weight, and people would consider feeding like breathing or elimination, a necessary but unexciting part of existence" (Saper et al. 2002). The fact that this is not the case suggests that there is a role for the reward systems in the brain in promoting motivational, hedonically driven feeding. Thus, excessive food intake may be explained more by dysfunction in the reward circuitry than strictly dysfunction in the homeostatic mechanisms controlling feeding habits. Studies in both humans and animals have supported the hypothesis that brain reward circuitry may be dysregulated in cases of obesity, disordered eating, and more recently, food addiction.

The neurocircuitry underlying eating behaviors is quite complicated. Of the multiple regions of the brain involved in the processes of food procurement and ingestion, there are four regions that stand out as also being activated during drug addiction: the amygdala/hippocampus, insula, orbitofrontal cortex, and striatum. These areas of the brain play key roles in learning the rewards associated with food, allocating attention and effort toward procuring food, setting incentive for food, and integrating internal homeostatic information about energy stores and gut contents (Blumenthal and Gold 2010).

Sensory input from the mouth is relayed to the same cortical areas of the brain that receive satiety signals from the gut (Rolls 2007). Limbic structures such as the thalamus then integrate hypothalamic energy control signals, largely under the control of gut hormones such as ghrelin, leptin, insulin, and peptide YY (Leibowitz and Hoebel 2004). The hypothalamus has direct connections to the nucleus accumbens, which is the control center for reward behaviors such as exercise, sex, and feeding. Mesolimbic dopamine (DA) directly acts upon the nucleus accumbens thereby controlling motivational and hedonic feeding as well as serving as the point of action for endogenous opioids, serotonin, and acetylcholine (ACh). It should be noted that these are some of the same neurotransmitters and pathways that control motivation and reinforcement of behaviors typically associated with substance addictions. The endogenous opioids modulate DA

release thereby affecting the reward process. Similarly, ACh in the nucleus accumbens has been associated with satiety, though the precise mechanism of action needs further investigation (Avena and Rada 2012). 5-HT is also associated with the sensation of satiety and can be associated with weight loss and fat intake (Halford and Blundell 2000). Given the interplay between all of these neurotransmitters and the nucleus accumbens, it is possible that dysfunction at any of these key points could result in disordered eating. This also explains why many of the pharmacological therapies for eating disorders have been targeting these neurotransmitter systems.

98.3 Obesity

Obesity, defined as a body mass index >30, has increased dramatically over the last three decades and is now estimated to affect over 33 % of the US population. Obesity is classified as a medical condition as it places a patient at increased risk for cardiovascular disease, diabetes, cancer, and other diseases resulting in a 5–20-year reduction in life expectancy, as well as costing $70–$100 billion annually by conservative estimates. The seriousness of these health consequences highlights the urgent need for strong prevention efforts and the development of effective treatment approaches for individuals with this condition (Volkow and O'Brien 2007).

The cause of obesity remains largely unknown, but, similar to eating disorders, is likely multifactorial (Fig. 98.1). It has been suggested that the behavioral phenotype of overeating may be influenced by an interplay of genetics, development, and environmental factors (Brownell and Gold 2012). While separable in theory, the interplay of one's genes; the time, place, and culture in which one lives; and the development of one's obesity through non-homeostatic mechanisms are likely all simultaneously involved and thereby relevant to the problem (Devlin 2007).

Within genetic theories, the "*thrifty genotype*" hypothesis suggests that the neurocircuitry underlying food procurement and bodily storage evolved at a point in human history in which food was scarce as a means of promoting survival in times of famine (Volkow and O'Brien 2007). However, recent advances in technology have allowed for the creation and modification of foods, which artificially enhance palatability beyond what would be found in nature, especially with regard to sugar, fat, and caloric value (Taylor et al. 2010). These calorie-rich, highly palatable foods are abundant and easily accessible in the typical Western diet. This combination of factors may lead to the activation of reward circuitry, which evolved to reinforce feeding behavior, and desires to engage in pathologic overconsumption, which would have been advantageous in a time of famine but now, in a context of abundance, appear maladaptive (Brownell and Gold 2012).

In contrast, the "developmental origin" hypothesis suggests that our exposure to certain nutrients and calorie contents in utero may imprint upon our developing brain and influence food choices when outside of the womb. Evidence to support this hypothesis comes from studies investigating the effects of consuming certain

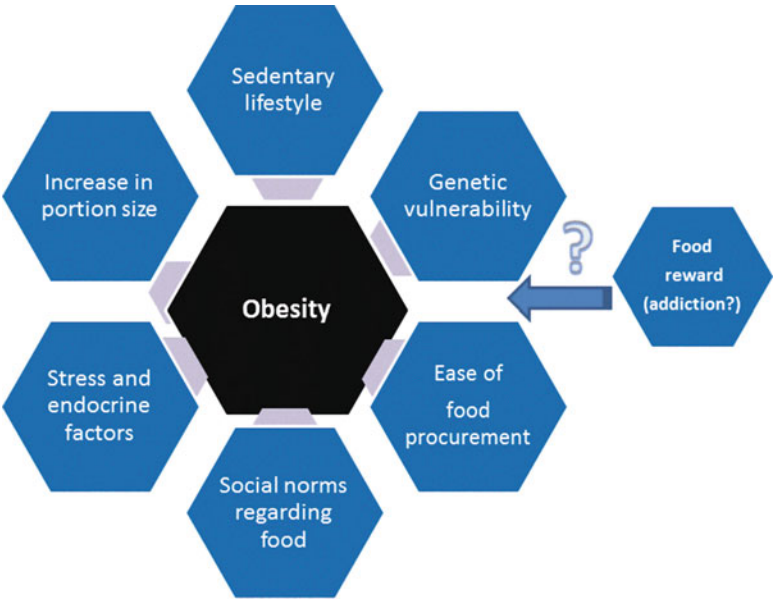

Fig. 98.1 Obesity is a multifaceted disorder with many contributing factors

diets during gestation on various outcome measures in the offspring. For example, recent research has found that the offspring of animals fed a high-fat diet during gestation are more likely to weigh more and consume more of a high-fat diet compared to controls (Bocarsly et al. 2012). While one hypothesis takes into account an evolutionary perspective and the other a more developmental view, both of these hypotheses may have value for understanding the current issues of obesity and disordered eating.

In regard to possible cultural and environmental influences of obesity, the past several decades have seen five major developments that are thought to have tipped the balance between caloric intake and energy expenditure to an unfavorable disproportion: (1) expanding labor market opportunities for women, (2) increased consumption of food outside of the home, (3) rising costs of healthy foods relative to unhealthy foods, (4) increasing quantities of caloric intake with declining overall food price, and (5) decreased requirements of occupational and environmental physical activity (Gold and Gold 2011). Other environmental factors implicated in the development of patterns of overeating include advertisements, sights, smells, and sounds, which have all been shown to induce food cravings and can result in overeating (Blumenthal and Gold 2010). Indeed, eating is more than a physiologic response; it can serve as a social lubricant, facilitating both personal and professional interactions, and is a prominent centerpiece for most individuals at holidays and celebrations (Gold et al. 2009).

These factors highlight the cultural aspect of obesity, but with them come a new set of challenges. During the Coronary Artery Revascularization in Diabetes (CARD) trial, which followed a population of 18–35-year-old patients over 10 years, the average patient showed a weight increase of at least 7 kg regardless of race and sex. This study demonstrated that significant weight gain over the course of adult life is now normative, suggesting a strong cultural component (Norman et al. 2003). In order to be classified as a disease, however, a condition must clearly differ from the norms of society. This conundrum has led some to refute claims that obesity should be included in the DSM-V as it may simply be a behavioral disturbance with an adverse medical outcome, not necessarily a psychiatric condition (Devlin 2007). While not all individuals who are obese may fit the existing criteria for food addiction, it is possible that individuals who do may represent a subcategory of obesity that is characterized in part by significant distress due to their thoughts and behaviors regarding food and/or exhibit comprised functioning as a result of these thoughts and behaviors. As such, these individuals may be recognized as having a psychiatric condition despite being within a weight range that may be considered relatively "normal" based on current trends within society. In fact, over- and/or normal-weight individuals also fit the criteria for food addiction.

Obesity is often described as an imbalance between caloric intake and energy expenditure. This simplified view has led some to suggest that obesity is the fault of the person due to excessive consumption, inadequate activity, or a combination of the two, resulting in much of the stigma that is associated with this condition (Devlin 2007). While decreased caloric consumption and increased physical activity can be effective in normalizing weight, these lifestyle modifications have proven very difficult to sustain (Volkow and O'Brien 2007). The failure of many lifestyle modifications to reduce obesity over the long term suggests that obesity may not be entirely a metabolic disorder, but likely has a neuropsychogenic component (Volkow and O'Brien 2007). While food addiction certainly does not explain all cases of obesity, the prevalence of people who eat for reasons other than obtaining energy suggests that other factors may play a role in motivating and/or reinforcing feeding behaviors. With the rapidly increasing number of cases of obesity, it may be time to consider new ways of understanding and approaching this problem.

Some hypothesize that obesity, at least in certain cases, is related to dysregulation of the brain's reward system. The hypothalamus is accepted as the primary brain region responsible for managing signals that regulate the intake of food, primarily through hormones such as ghrelin, leptin, and insulin which effect both the hypothalamus and the reward neurocircuitry in such areas as the caudate nucleus, hippocampus, and insula (Taylor et al. 2010). Food, especially when it is rich in fat and sugars, stimulates brain reward circuitry, in part, through the release of endogenous opioids, cannabinoids, and DA (Abizaid et al. 2006). Since these are some of the same neuropathways and neurotransmitters associated with drug addiction, as mentioned earlier, some have suggested that repeated exposure to certain foods in vulnerable individuals may result in compulsive food consumption, poor control, conditioning to food stimuli, and ultimately excess weight gain

(Volkow and O'Brien 2007). Further evidence of neurochemical similarities between substance addiction and obesity comes from studies showing that like individuals with drug addiction, obese individuals have decreased striatal D2/D3 receptor availability and demonstrate elevated levels of DA metabolism (Corwin and Grigson 2009; Wang et al. 2009). Such findings suggest dysfunction within the brain reward mechanisms of individuals with obesity.

Stimulant drugs such as methamphetamine or cocaine are known to curb appetite presumably by affecting the reward circuitry, while partial blockade of these same pathways by antipsychotics has been associated with overconsumption thereby increasing the risk for obesity and metabolic syndrome (Volkow and O'Brien 2007). Taken together, current evidence suggests that similar neurological pathways are associated with both addiction and obesity. Thus, medications used to treat drug addiction, including cannabinoid antagonists; opioid antagonists, such as naloxone; GABA agonists, such as baclofen; and corticotropin-releasing hormone antagonists, such as CRF-1, have been suggested for the treatment of obesity, as have some of the same behavioral interventions, including cognitive behavioral therapy (CBT), cognitive behavioral therapy with guided self-help (CBT-gsh), dialectical behavioral therapy (DBT), and interpersonal therapy (IPT), incentive motivation, and 12-step programs (Volkow and O'Brien 2007; Yarnell et al. 2013).

The addictive behaviors underlying some cases of obesity may be hardwired. There have been reports of a subset of patients who have undergone bariatric weight loss surgery for obesity and therefore are less likely to be able to consume food in excess, later developing other addictive behaviors such as gambling, substance abuse, and impulsive spending (Wendling and Wudyka 2011; Conason et al. 2012). Interestingly, sweet preference has also been shown to correlate with a paternal history of alcoholism. In fact, one study found that having a family history of alcoholism increased the chance that one preferred a stronger sweet taste by five times (Kampov-Polevoy et al. 2003). Though this association requires further investigation, the implication of these findings is that the tendency toward increased reward sensitivity, which may lead to addiction, may be intrinsic (Taylor et al. 2010).

98.4 Binge Eating

Binge eating disorder is now listed in the DSM V as a stand alone diagnosis. Binge eating is characterized by eating rapidly, eating more than was intended, eating alone, and feelings of disgust, guilt, or depression secondary to these binges. It has been reported that 3.5 % of adult women and 2 % of adult men within the US population suffer from binge eating disorder. These numbers are reported to be slightly lower for adolescents (2.3 % females, .8 % males) (Smink et al. 2012).

Bingeing has long been associated with bulimia nervosa, as binge eating is one of the major diagnostic criteria for this disorder, but it is also associated with obesity (APA 2013). The key difference between binge eating and bulimia

nervosa is that binge eating disorder patients do not engage in compensatory behaviors (i.e., vomiting, laxative use, excessive exercise) to expel calories after consumption. Thus, the excess caloric intake is not compensated for, which may result in weight gain. Indeed, one study found that nearly 70 % of participants with binge eating disorder were obese and 20 % were overweight (Grucza et al. 2007). A larger, national study found obesity to have a lower prevalence rate among individuals who had ever had binge eating disorder. However, this number was still relatively high, with approximately 40 % of these individuals considered either obese or severely obese (Hudson et al. 2007).

Many studies have attempted to elucidate the relationship between binge eating and obesity. Longitudinal studies have demonstrated a correlation between binge eating and significant non-developmentally appropriate weight gain in adolescents and young adults (Tanofsky-Kraff et al. 2006). Further, one study demonstrated a correlation between binge eating and both being obese and gaining weight over a 20-year span (Hasler et al. 2004). Another study also shows that cessation of binge eating is associated with weight loss, while continued binge eating is associated with ongoing weight gain (Devlin et al. 2005). Studies such as these strongly suggest a connection between uncompensated binge eating and weight gain and suggest that binge eating could ultimately contribute to obesity (Devlin 2007). It is thus reasonable to suggest that normal-weight individuals with binge eating disorder may be at risk for obesity.

In addition to the association between binge eating and obesity, binge eating has several similarities to addiction. Some of the criteria used to identify disorders characterized by binge eating are remarkably similar to those used to assess substance dependence. These include (1) binge-type intake, defined as consuming a larger amount of food than typically considered normal in a discrete period of time, (2) a sense of lack of control over eating during a binge episode, and (3) marked distress regarding binge eating. In fact, binge eating has been described as including "compulsion, marked change in affect, and long-term harm, " and it is noted that "physiologically based satiety tolerance enables escalation of food 'dose'" (Rogers 2011).

The types of foods consumed during binge episodes are typically those that should be consumed in moderation due to their high-fat, high-calorie, and high-sugar content (Kales 1990). Consuming foods rich in sugar and fat activates the reward circuitry of the brain, as mentioned earlier. Bingeing on both high-sucrose and high-fat foods has been shown to elicit DA release in the nucleus accumbens in animals (Avena et al. 2012a). Animal models have also shown that bingeing is associated with downregulation of D2-receptor mRNA and an increase in D3-receptor mRNA in the nucleus accumbens (Spangler et al. 2004). Interestingly, these dopaminergic changes seen in response to bingeing are the same as those observed in obesity and drug dependency (Johnson and Kenny 2010; Koob and Volkow 2010). This has led some to speculate that binge eating of palatable foods may result in neurochemical changes and subsequent addictive-like behaviors (Avena et al. 2012a).

Studies such as these have also led some to wonder if the dopaminergic system could provide a target for pharmaceutical intervention of bingeing behaviors. Indeed, one study using an animal model of binge eating found the D2 antagonist, raclopride, reduces binge intake of high-fat foods, while having no effect on ad libitum consumption (Corwin and Wojnicki 2009). Similarly, studies suggest that naltrexone, an opioid antagonist, can suppress bingeing behaviors (Corwin and Wojnicki 2009). Further, single-photon emission tomography (SPECT) studies have demonstrated that when compared to obese controls, decreased 5-HT transporter binding was found among obese binge eaters, suggesting that this may be another potential pharmaceutical target (Kuikka et al. 2001).

Within the brain, the ventral limbic circuit and the orbitofrontal cortex are important in the regulation of feeding behaviors as well as identifying emotional stimuli and facilitating a subsequent response, and atrophy or deregulation within these regions has been noted in persons with bingeing behaviors (Marsh et al. 2009). This suggests a link between emotions and binge eating. Indeed, one study found that 100 % of participants, all of whom were obese women who binge eat, reported that mood contributed to binge behavior. 68 % reported depression or sadness and 55 % reported boredom preceding a binge episode (Chua et al. 2004). It is not surprising, therefore, that the teaching of affect regulation skills through the use of dialectical behavioral therapy (DBT) has yielded promising results in this population (Telch et al. 2001).

98.5 Screening Individuals for Food Addiction

Given the potential magnitude and severity of food addictions, efforts have been made to develop screening tools for addictive-like eating. Gearhardt et al. (2009a) created the Yale Food Addiction Scale (YFAS), which consists of a series of questions based on the substance addiction criteria as outlined in the DSM-IV. This tool is designed to identify and better characterize signs and symptoms consistent with food addiction. Respondents use a yes/no format and 5-point Likert scale for questions regarding frequency. In early testing, the YFAS exhibited adequate internal reliability, good convergent validity with other measures of disordered eating, as well as good discriminant validity relative to related yet dissimilar conditions such as alcohol consumption and impulsivity (Gearhardt et al. 2009b). A recent study has shown a link between YFAS scores and mood disorders among obese patients with binge eating disorder. The YFAS has also been shown to be a good predictor of the frequency of binge eating episodes in this patient population (Gearhardt et al. 2012). As noted by the authors, the YFAS may help clinicians better identify disordered eating habits in their patients as well as allow researchers to better identify potential candidates for future studies. Future studies in this area may facilitate the development of screening tests for addiction to specific food ingredients, such as fat or sugar, which may lead to a better understanding of the types of foods that may be associated with food addiction, as well as the development of more specific approaches to treatment.

98.6 Management of Food Addiction

The study of food addiction is relatively new and specialized treatment approaches have not yet been developed. However, because of overlaps between binge eating, obesity, and food addiction, it is possible that strategies that are effective for treating binge eating and obesity may also prove helpful in the treatment of food addiction. Certain types of psychotherapy, including cognitive behavioral therapy (CBT), cognitive behavioral therapy with guided self-help (CBT-gsh), and interpersonal therapy (IPT), have shown success in the treatment of binge eating disorder (Devlin et al. 2005; Iacovino et al. 2012). As mentioned earlier, DBT has also been shown to be effective in treating binge eating behavior (Telch et al. 2001). Among existing pharmaceuticals, fluoxetine, desipramine, imipramine, and topiramate have been suggested to be effective in the treatment of binge eating disorder (Walsh et al. 1997), and phentermine, diethylpropion, and orlistat are often provided for obesity (Powell et al. 2011). For some, binge eating may become an ingrained behavior that serves as a form of self-medication in response to negative emotional states such as depression, anxiety, loneliness, boredom, anger, and interpersonal conflict. This highlights the role of behavior modification, in addition to pharmacological interventions, in the treatment of food addictions (Taylor et al. 2010). It should be noted that treatment of disordered eating can be a long and arduous process marked by alternating periods of relapse and recovery.

With regard to obesity, some patients turn to invasive procedures such as bariatric surgical treatments including gastric bypass and gastric banding. While these procedures do result in dramatic weight loss, they can be expensive and can have significant risks, including the development of gastric dumping syndrome and increased risk of bone fractures (Nakamura et al. 2011). As a result, much attention today is focused on developing better treatment options. Given the rise of obesity not only in the USA but around the world (Yach et al. 2006), a number of pharmaceutical companies are looking to develop new treatments for obesity based on the addiction hypothesis (Blumenthal and Gold 2010). Indeed, a number of new treatments are in both phase II and phase III clinical trials (Blumenthal and Gold 2010). The majority of these potential treatment options target the neuropathways and neurotransmitters discussed in this chapter, including raclopride, bupropion, and antipsychotics which target dopamine; naltrexone, naloxone, and nalmefene which target the opioid system; baclofen and topiramate which target the GABAergic system; SR141716, AM 251, and rimonabant which target cannabinoid receptors; as well as several new pharmaceuticals (Berner et al. 2011; Yarnell et al. 2013). However, these medications are not without risk; many of these drugs carry significant side effects including increased risk for depression, anxiety, obsessive-compulsive disorder, seizures, suicide, confusion, or memory deficits (Blumenthal and Gold 2010). Given the risks and side effects associated with these drugs, physicians will need to exercise great care when considering whether to prescribe these treatments and should carefully select their population base prior to prescribing (Blumenthal and Gold 2010).

98.7 Conclusion

As it stands, obesity and binge eating behaviors will continue to be a threat to global health (Avena et al. 2012c). As such, it is perhaps time to reevaluate the current food environment from many aspects while taking into consideration both the individual's perspective and society as whole. Societal measures may, in fact, be required at this time as dysfunctional eating behaviors affect not only the current generation but also its offspring due to the effects that consuming certain highly palatable foods may have on the developing brain in utero.

Given that some of the cultural factors discussed in this chapter are driven by economic factors that lie outside the control of the individual, the topic of obesity cannot simply be relegated to the domain of personal responsibility. Rather, economic incentives that may encourage people to make unhealthy food choices may need to be reevaluated on a larger scale. Indeed, any plan to combat the rise in obesity will need to address the economic, political, social, psychological, and biological factors that contribute to obesity, as well as factors such as taste, accessibility, convenience, cost, and level of promotion (Yach et al. 2006). Moreover, society may need to closely reevaluate the current state of food marketing. As mentioned earlier, one study has found that food-addicted persons respond at an even higher level to food cues than their nonaddicted counterparts (Gearhardt et al. 2011). This finding suggests that advertising cues may contribute, at least in part, to compulsive eating in at-risk persons. Further, societal changes such as reevaluating where government subsidies are allocated, taxation, publicly enforced well-care programs, and corporate-driven employee well-being programs may also be needed to address the issues of disordered eating and obesity. While these efforts are not expected to cure obesity, binge eating, or food addiction, they may help to reduce their prevalence and aid prevention efforts.

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Section VIII

Medical Disorders and Complications of Alcohol and Other Drugs, Pain and Addiction

Jag H. Khalsa and Paul S. Haber

Medical Disorders and Complications of Alcohol and Other Drugs, Pain and Addiction: An Introduction

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Jag H. Khalsa and Paul S. Haber

The health consequences of drugs are major problems throughout the world with billions of people using legal (tobacco and alcohol) and illegal drugs (amphetamines, cocaine, opiates, hallucinogens, and marijuana). Drug use is associated with burdensome social, economic, and health consequences, the latter involving almost every physiological/biochemical system. These may include psychiatric, cardiovascular, metabolic, and hepatic complications and infectious diseases. Although there is a myriad of problems related to drug use, it is the medical consequences that are the leading causes of death, and consequently, these are of great medical concern. It is evident that this section on medical consequences of drug abuse is an important component of a comprehensive textbook of addiction medicine that should describe, most if not all, these health effects and their clinical management. In general, the principles of assessment and management of these disorders are no different from people who do not abuse drugs or alcohol, but this section of the textbook describes particular patterns of morbidity and approaches to management that distinguish this population.

The typical patient with a substance use disorders has multiple problems rather than single pathology as described above, yet it is not generally feasible for multiple specialists to become involved. Consequently, the addiction medicine specialist needs a broad range of clinical skills to adequately manage patients with complex health problems including pain. Alcohol and other drugs particularly affect the

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neurological and gastrointestinal systems but may involve all other systems. The chief medical comorbidities include infectious diseases, sleep, and pain disorders. Patients may be infected with infections including human immunodeficiency virus (HIV) and hepatitis C virus (HCV), tuberculosis, and sexually transmitted infections individually or in combination. Nutrition is important and nutritional disorders may impact on recovery from other co-occurring illnesses. Patients often require complex treatment with multiple medications, and consequently, pharmacokinetic/pharmacodynamic drug-drug interactions are a particular challenge in this population. Physicians with a background in mental health will welcome a concise description of the chief medical disorders to be encountered in their patients. In many cases with pathology that responds to management as recommended in this section, further specialist referral can be minimized.

Infectious diseases form the focus of several chapters in this section. An estimated one third of the global population of seven billion is living with one or more bacterial or viral infections (United Nations AIDS (UNAIDS) 2008). There are an estimated 200 million people who abuse illegal drugs regularly (United Nations Office on Drugs and Crime: World Drug Report 2007) in the world, and this population is at increased risk of blood-borne viruses and other infections. Legal and illegal substance abuse alone costs the American society an estimated 534 billion dollars annually (Office of National Drug Policy 2004), while diabetes and cancer cost an estimated $174 billion (American Diabetes Association 2003) and $263 billion (American Cancer 2008), respectively. Infections that occur in people who use substances lead to enormous social, economic, and health costs to the society. These infections are associated with inferior outcomes in drug users compared to nondrug users for a range of reasons including poor general health, poor engagement with health care, lower rates of treatment uptake, and higher rates of treatment dropout. Alcohol and drug use are also associated with impaired immune function that may increase infection risk. Infectious diseases complicating drug use can affect all systems of the body and are described throughout this section, but the blood-borne viruses are particularly important public health problems. There have been striking advances in the treatment of blood-borne virus infections particularly HCV and HIV. New antivirals have transformed HCV treatment and are poised to rapidly develop further in the coming decade. The complications and management of viral hepatitis in drug-abusing populations, particularly HCV, have been addressed by Giorgio Barbarini. HIV treatment continues to improve in efficacy and tolerability. It is important to note that the problem of drug interactions that appeared earlier between HIV antiretrovirals and methadone seems to be less with the newly approved buprenorphine. Khalsa and his colleagues have reviewed the medical consequences of substance abuse and co-occurring infections and how to clinically manage these health effects.

The cardiovascular complications of alcohol and other drugs have been addressed by Mori Krantz et al. This group has provided an overview on the

broad range of cardiovascular issues including both the pathophysiological approach and practical approach for clinicians. Patients who require surgery present particular challenges. Spies and colleagues provide an overview of the perioperative management problems in people with substance use disorders.

Neurological complications include neuropsychiatric complications such as anxiety disorders, severe depression, and suicidal attempts. Alcohol in particular is a major cause of many of the common neurological disorders including seizures, confusional states, stroke, and peripheral neuropathies. Bough and colleagues describe these disorders and their management. Crome and colleagues focus on memory and cognitive function, which is often the most critical functional impairment in the addicted patient.

Gastrointestinal and liver disorders are commonly seen in the substance-using population particularly in those that misuse alcohol. Alcoholic liver disease is the leading cause of death in those with alcohol dependence and is a major focus of the chapter by Haber and colleagues. Hepatitis C is now the leading indication for liver transplantation and a major public health problem. New antiviral treatment offers great promise over the next decade to increase the cure rate and reduce the morbidity associated with current interferon-based treatment.

There are myriad endocrine changes associated with alcohol and drug use. These include direct action of drugs on endocrine tissues and secondary effects related to infectious diseases, nutrition, and adverse effects from prescribed medications. All classes of abused drugs are associated with endocrine effects particularly alcohol, psychostimulants, and opioids as described by Dobs and Hallinan in respective chapters. Sexual dysfunction is a particular issue and is another clinical problem that may be overlooked in clinical practice. Hallinan describes the common disorders of sexual function and present a clinical approach to their management.

The kidney may be affected by substance abuse in a range of direct and indirect ways. Hennessy provides an overview of the clinically important syndromes and outlines their management.

Disturbed sleep is a very common yet sometimes overlooked complication of substance abuse. It may contribute to relapse and drug seeking as patients often increase use of their primary drug or use other drugs to restore adequate sleep. Varenbut and colleagues provide a sleep medicine overview, with specific emphasis on sleep physiology and the psychiatric and addictive disorders causing sleep concerns. Clinical and laboratory assessment is described. A practical approach is offered for the treatment of sleep disorders with both pharmacotherapy and cognitive behavioral therapy approaches.

In summary, drug abuse and co-occurring infections of HIV and HCV are associated with a wide variety of serious health effects. Although treatment of drug addiction, its medical consequences, and the dual infections of HIV and HCV are complex, good clinical outcomes are achievable with integrated programs of health care.

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Cardiovascular Consequences of Addiction

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Peter K. Moore, David Kao, and Mori Krantz

Contents

Abstract

Drugs of abuse often have important effects on the cardiovascular system, some of which are life-threatening. An understanding of the intersection between addictive and cardiovascular disorders, therefore, is increasingly relevant to general practitioners and psychiatrists. The effects of illicit drugs vary depending upon the agent, dose, route of administration, and its potential interaction with other prescription medications. Cardiovascular consequences can range from innocuous side effects, such as mild tachycardia and hypertension, to life-threatening ventricular arrhythmias and myocardial infarction.

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Hemodynamic alterations are common with both active drug abuse and withdrawal and are frequently mediated by the autonomic nervous system.

Sympathomimetic drugs like amphetamines and cocaine often result in an increase in blood pressure and heart rate. In addition, they may cause substantial cardiotoxicity including arrhythmia, stroke, myocardial infarction, heart failure, and death. These stimulant drugs often increase the propensity for developing atherosclerosis. Some of this is mediated by increases in blood pressure and lipids, but may also occur due to proinflammatory effects or increased hypercoagulability. By contrast, some drugs such as opioids lead to small reductions in pulse and blood pressure. Most naturally occurring opioids do not alter cardiac rhythm; however, synthetic opioids, such as methadone, may result in QTc interval prolongation and torsades de pointes, a form of life-threatening ventricular arrhythmia. In this chapter we review the cardiovascular effects of common drugs of abuse including cocaine, amphetamines, nicotine, opioids, alcohol, marijuana, and anabolic steroids.

100.1 Introduction

Drugs of abuse have a myriad of cardiovascular effects. Depending on the drug, dose, and route of administration, cardiovascular consequences can range from innocuous side effects, such as mild tachycardia and hypertension, to life-threatening ventricular arrhythmias and myocardial infarction (Table 100.1). Hemodynamic alterations are common with drug use and most often are mediated through interactions with the autonomic nervous system (Ghuran and Nolan 2000). Sympathomimetic drugs like amphetamines cause an increase in release of peripheral catecholamines stimulating increases in heart rate, systemic vascular resistance, and cardiac contractility, thus resulting in augmentation of cardiac output and blood pressure. In contrast, several drugs are directly cardiodepressant in the acute setting, and many drugs of both types are cardiotoxic causing cardiomyopathy and congestive heart failure with long-term use.

Changes in the balance of myocardial oxygen supply and demand with drug use can lead to myocardial ischemia (Ghuran and Nolan 2000). For example, cocaine augments oxygen demand in the myocardium by increasing heart rate, afterload, and contractility while simultaneously decreasing supply by inciting epicardial coronary vasoconstriction. Modulation of lipid profiles, coagulation factors, platelet function, and inflammation further heighten the risk of cardiac ischemic events in patients using these drugs.

Many recreational drugs are arrhythmogenic in the acute setting or during abstinence/withdrawal. Mechanisms of arrhythmias are complex and likely result from interplay between the direct effects of drugs, electrolyte derangements, sympathetic nervous alterations, and cardiac ischemia. Of particular importance is the interaction of several drugs, especially the synthetic opioids, with a subunit of a voltage-gated potassium channel coded by the human Ether-à-go-go-Related Gene (hERG) (Katchman et al. 2002). Inhibition of this subunit causes alterations

Table 100.1 Cardiovascular effects of various drugs of abuse

Drug	Cardiovascular effect
Ethanol	Hypertension
	Arrhythmias – holiday heart
	Dilated cardiomyopathy
	Coronary artery disease
	Stroke
Cocaine	Tachycardia
	Hypertension
	Myocardial depression
	Prothrombotic risk
	Atherosclerotic risk
	Chest pain
	Angina pectoris
	Myocardial infarction
	Arrhythmias
	Left ventricular hypertrophy
	Dilated cardiomyopathy, myocarditis
	Aortic dissection
	Infective endocarditis
	Stroke
	Mesenteric ischemia
Amphetamines	Tachycardia
	Hypertension
	Chest pain
	Myocardial infarction
	Arrhythmias
	Sudden cardiac death
	Aortic dissection
	Cardiomyopathy
	Infective endocarditis
	Stroke
	Premature coronary artery disease
Opioids	Orthostatic hypotension
	Ischemic preconditioning
	Ventricular arrhythmia
	Infective endocarditis
Nicotine	Coronary artery disease
	Worsens angina pectoris
	Myocardial infarction
	Stroke
	Prothrombotic risk

(*continued*)

Table 100.1 (continued)

Drug	Cardiovascular effect
Cannabis	Tachycardia
	Bradycardia
	Hypertension
	Orthostatic hypotension
	Syncope
	Worsens angina pectoris
	Myocardial infarction
	Ischemic stroke
	Arrhythmias
Anabolic steroids	Prothrombotic risk
	Hypertension
	Dyslipidemia
	Myocardial infarction
	Ischemic stroke
	Ventricular hypertrophy

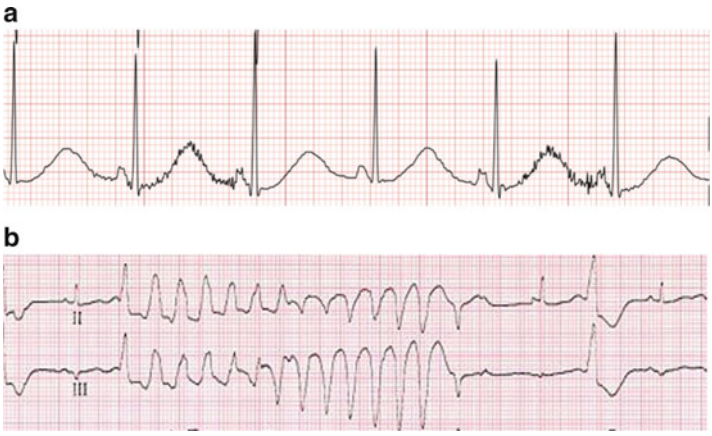

Fig. 100.1 (**a**) Prolonged rate-corrected QT interval (QTc). (**b**) Torsades de pointes, a type of polymorphic ventricular tachycardia

in repolarization during phase 3 of the action potential, which can lead to acquired prolongation of the rate-corrected QT (QTc) interval, augmenting the risk of the ventricular arrhythmia, torsades de pointes, and sudden cardiac death (Fig. 100.1).

This overview highlights the variety of short-term and long-term cardiovascular consequences of abused drugs, with a particular focus on cocaine, opioids, and alcohol employing a clinical vignette format.

100.2 Mechanisms and Cardiovascular Consequences of Abused Drugs

100.2.1 Alcohol

Alcohol (ethanol) is widely used throughout the world with an estimated two billion users representing nearly half of the world's population. Light to moderate alcohol consumption has been associated with a reduced risk of atheroembolic vascular events including myocardial infarction and ischemic stroke, but chronic heavy alcohol use is clearly cardiotoxic and is associated both directly and indirectly with a number of cardiovascular consequences including hypertension, atrial fibrillation, stroke, and cardiomyopathy. Adverse cardiovascular effects begin to appear with consumption of two to three standard drinks/day or more and increase thereafter in a dose-dependent fashion (Lange and Hillis 2012). In comparison with moderate regular drinking, binge drinking is also associated with increased risk of complications such as atherosclerosis, atrial fibrillation (AF), and stroke (Liang et al. 2012). Alcohol is directly toxic to cardiomyocytes via a number of mechanisms including uncoupling of the excitation-contraction system, impairment of calcium sequestration in the sarcoplasmic reticulum, reduction of mitochondrial respiratory ratio, and increased interstitial protein synthesis (George and Figueredo 2011; Lange and Hillis 2012). In addition, alcohol increases sympathetic tone producing elevated heart rate and blood pressure (Mandyam et al. 2012), impairs vagal tone, may precipitate electrophysiologic changes in atrial tissue (Kodama et al. 2011), and is associated with endothelial dysfunction (Goslawski et al. 2013), each of which may contribute to adverse cardiovascular outcomes.

Abstinence often results in rapid improvement in many of cardiovascular consequences and in some cases may be the only intervention necessary in the long term to address alcohol-associated cardiovascular risk. However, acute alcohol withdrawal delirium tremens in particular can precipitate cardiovascular changes that may be fatal. Hypertension and tachycardia are classic symptoms of acute alcohol withdrawal, and though they improve within 3–4 days of alcohol cessation, they may precipitate ischemic or hemorrhagic stroke, acute decompensated heart failure, or cardiac ischemia in the setting of coronary artery disease. Fatal arrhythmias may also be precipitated by adrenergic surge, electrolyte deficiencies, or QT interval prolongation. Management of patients with acute alcohol withdrawal who have known cardiovascular disease is further complicated by potential exaggerated hemodynamic responses to beta-blockers, calcium channel blockers, and long-acting nitrates early in the course of withdrawal (Kahkonen 2006). There is little direct evidence regarding management of cardiovascular complications of acute alcohol withdrawal in the setting of specific cardiac conditions, but propranolol and clonidine are most commonly suggested to treat withdrawal-related autonomic instability as well as aggressive replacement of potassium, magnesium, and phosphate. Because of the potential exaggerated effects on cardiac output and peripheral vascular resistance of both medications, particular caution must be taken in the setting of dilated cardiomyopathy and valvular disease such as advanced aortic stenosis.

Vignette *A 48-year-old man is evaluated in the emergency department on January 2 for intermittent palpitations and chest pressure over the preceding 48 hours. He does not regularly receive medical care and takes no medications. He smokes cigarettes but uses no other drugs. He reports drinking up to 12 packs of beer per day normally and consumed up to double his normal amount during the week prior to presentation. He is noted to have an irregular heart rate of 130, a blood pressure of 140/90, and moderate pedal edema.*

100.2.1.1 Atrial Fibrillation

Atrial fibrillation (AF) is the most common arrhythmia among older adults and is categorized as paroxysmal (intermittent, not exceeding 7 days), persistent (episodes exceed 7 days or require treatment to terminate), and permanent (continuous, long standing) (Fig. 100.2). AF was the most common arrhythmia identified in 1978 as part of the "holiday heart syndrome" that was defined as hospital admission for dysrhythmia immediately following binge drinking in the setting of chronic alcohol use, classically following a weekend, vacation, or year-end holiday (Ettinger et al. 1978). Since then, moderate to heavy drinking has been associated with both new onset AF and exacerbation of existing paroxysmal AF, and it is suspected that alcohol is a causative factor in up to two-thirds of patients $\leq$65 years of age with AF (Samokhvalov et al. 2010; Kodama et al. 2011; Liang et al. 2012; Mandyam et al. 2012). However, the mechanisms underlying this association remain unclear, though clear electrophysiologic changes have been noted in atrial tissue exposed to ethanol including shortening of the action potential duration and refractory period, each of which may trigger dysrhythmia. The increased incidence of atrial fibrillation may also be due to other factors such as heightened sympathetic tone or electrolyte disturbances. Alcohol consumption is often associated with hypokalemia and hypomagnesemia, which both lead to QTc interval prolongation in experimental models. Heavy alcohol consumption has also been associated with left atrial enlargement and left ventricular enlargement (Singh et al. 2013), both of which may increase the risk of developing AF.

Acute AF related to alcohol and/or illicit drug use will often revert to sinus rhythm without requiring electrical cardioversion in young patients (Krishnamoorthy et al. 2009). However, if the patient is likely to continue to use alcohol, they will remain at an elevated rate of future episodes of paroxysmal AF that may become permanent. There are no specific recommendations regarding management of AF related to alcohol use. β-blockers have a theoretical advantage over calcium channel blockers for rate control in light of the adrenergic excess

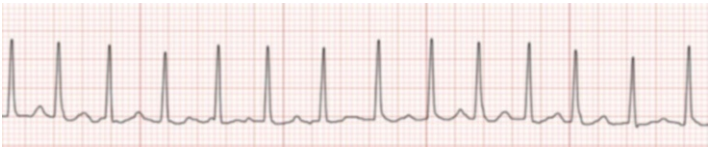

Fig. 100.2 Atrial fibrillation

thought to contribute to alcohol-related AF. Alcohol and drug abuse have been associated with a lower likelihood of treatment with warfarin, and it remains important to risk stratify all patients using a validated risk score such as the $CHADS_2$ or CH_2ADS_2-Vasc score when deciding whether to initiate prophylactic antiplatelet or anticoagulation therapy (Camm et al. 2010). Unlike warfarin, newer agents such as rivaroxaban, dabigatran, or apixaban offer the advantage of not requiring routine monitoring, which may be useful in the setting of questionable compliance (Camm et al. 2012). These agents were associated with lower rates than warfarin of intracerebral hemorrhage and gastrointestinal bleeding, both of which occur more frequently in alcoholics than nonalcoholics, but there is no direct evidence to determine whether they provide a safe alternative for anticoagulation in AF in the setting of alcohol abuse.

100.2.1.2 Hypertension and Vascular Disease

Alcohol has been associated with dose-dependent increase in blood pressure both acutely and chronically in both men and women in several large studies (Marmot et al. 1994; Yoshita et al. 2005; Wakabayashi and Araki 2010). While the effect was seen at all ages, it was more prominent in the elderly where the propensity for hypertension is elevated. Furthermore, abstinence has been associated with clinically meaningful reductions in blood pressure comparable with effects of antihypertensive medications (Estruch et al. 2005). The mechanism of the association between alcohol and hypertension is incompletely understood, although evidence of vascular dysfunction has been observed even in young binge drinkers (Goslawski et al. 2013). Marked endothelial dysfunction is observed in alcoholics that is only partially reversed with abstinence, suggesting a persistent risk of cardiovascular morbidity and mortality. Furthermore, patients may continue to demonstrate exaggerated blood pressure response to stress for many weeks. Nevertheless, complete abstinence has been associated with reduction in systolic blood pressure of 7–12 mmHg approximating the effects of the most potent antihypertensive drugs. Therefore, abstinence remains a primary recommendation for all patients with hypertension who use alcohol.

The association between alcohol and vascular disease including coronary artery disease and stroke is J-shaped, with small to moderate amounts of ethanol producing reductions in several cardiovascular outcomes due in part to favorable effects on high-density lipoprotein cholesterol and apolipoprotein A–I levels, inhibition of platelet aggregation, increased antioxidant activity, decreased serum fibrinogen, anti-inflammatory effects, and improved fibrinolysis. However, heavy alcohol use is associated with increases in atherosclerotic coronary artery disease (McElduff and Dobson 1997; McClelland et al. 2008; Ruidavets et al. 2010), ischemic stroke, and cerebral hemorrhage (Leppala et al. 1999) compared with moderate drinkers. The mechanism of this association remains controversial but is likely due in part to increased serum triglycerides, hypertension, decreased nitric oxide synthesis, and increased inflammation (Cahill and Redmond 2012). In particular, risks of both coronary and cerebrovascular events have been repeatedly shown to be increased by binge drinking (Snow et al. 2009; Ruidavets et al. 2010), and an acute increase in

stroke risk within 1–24 h of heavy alcohol use has been observed. This may be due to reactive thrombocytosis and increased platelet aggregation during alcohol withdrawal, and we speculate that increased adrenergic activity may also play a role. Paradoxically, the observed association between alcohol and hemorrhagic stroke may relate to impaired coagulation function as well as weakening of cerebral arteries. The increased risk of both stroke and death due to ischemic heart disease appears to return toward baseline in former heavy drinkers (Hillbom et al. 1999; Roerecke et al. 2011), and apart from abstinence, there are no specific risk reduction strategies recommended apart from standard cardiovascular risk reduction. Elimination of tobacco abuse may be a particularly important risk factor given that it is often used in the setting of social alcohol consumption and is itself a potent atherosclerotic risk factor.

100.2.1.3 Cardiomyopathy

Although light to moderate alcohol consumption has been associated with a lower rate of heart failure than nondrinkers, chronic heavy alcohol use is a well-known cause of left ventricular diastolic and systolic dysfunction. In fact, alcohol may be the leading etiology of nonischemic dilated cardiomyopathy in industrialized nations. Most men who develop alcoholic cardiomyopathy have consumed $\geq$8 standard drinks/day for $\geq$5 years. Women appear to be more sensitive to the cardiotoxic effects of alcohol and may develop cardiomyopathy with a smaller comparative exposure. Evidence of cardiotoxicity may be apparent long before the emergence of symptoms, as 30–50 % of alcoholics have echocardiographic evidence of left ventricular hypertrophy and/or diastolic dysfunction and 30 % of asymptomatic alcoholics have evidence of systolic dysfunction as measured by reduced left ventricular ejection fraction (LVEF). Direct myocardial damage may be mediated by acetaldehyde, the first metabolite of ethanol. Acetaldehyde levels are particularly elevated in heavy drinkers, in part due to reduce hepatic aldehyde dehydrogenase activity (Zhang et al. 2004). Chronic activation of the renin-angiotensin-aldosterone system and sympathetic nervous system and nutritional deficiency (especially thiamine) may also contribute to progression of myocardial dysfunction by potentiating alcohol- and acetaldehyde-induced cell death.

Abstinence can result in significant improvement in left ventricular systolic function if achieved early during the progression of myocardial dysfunction. It has been shown that "controlled" intake of two to six standard drinks/day has also been associated with improvement in LVEF within months, but because controlled drinking is generally not possible for alcoholics, total abstinence remains the primary recommendation. Long-term survival in patients with alcoholic cardiomyopathy who achieve abstinence is the same or better than patients with idiopathic dilated cardiomyopathy, whereas patients who continue to drink have a lower survival (Prazak et al. 1996). As for all dilated cardiomyopathies, neurohormonal blockade with β-blockers and renin-angiotensin-aldosterone system inhibitors is the cornerstone of medical therapy. Additional considerations in the setting of alcoholic cardiomyopathy are nutritional and vitamin supplementation, particularly vitamin B12 and folate.

Vignette *During his hospitalization, the patient is noted to be in atrial fibrillation and to have reduced LVEF of 40 %. Cardiac catheterization reveals no coronary artery disease. He is counseled on abstinence; started on β-blockers, an angiotensin-converting enzyme (ACE) inhibitor, warfarin, and loop diuretics; and then discharged to an addiction treatment center. He leaves treatment after 21 days of a 30-day program and is found dead two weeks later in a hotel room. Although there are empty bottles of alcohol in his room, his blood alcohol level is found to be zero. Autopsy revealed an enlarged, hypertrophic heart but no evidence of acute ischemia, consistent with sudden cardiac death.*

100.2.1.4 Sudden Cardiac Death

Large studies have demonstrated an elevated risk of sudden death associated with heavy drinking (>6 drinks/day), even in patients without preexisting ischemic or structural heart disease (Wannamethee and Shaper 1992). Electrophysiologic studies have demonstrated that alcohol increases susceptibility to ventricular arrhythmias as well as supraventricular arrhythmias. However, sudden death may also occur during periods of abstinence or withdrawal. The QTc interval is may be prolonged in up to 63 % of cases during alcohol withdrawal (Cuculi et al. 2006) and normalizes with remission of abstinence symptoms. Electrolyte abnormalities, catecholamine excess, impaired vagal control of heart rate, myocardial fibrosis, and sleep apnea may also contribute to a heightened risk of arrhythmia (Laonigro et al. 2009).

In addition to correction of electrolyte abnormalities, particularly hypokalemia and hypomagnesemia, it is therefore important to consider cardiac monitoring of patients during the early stages of withdrawal, particularly in the setting of underlying structural heart disease and severe symptoms including delirium tremens. Furthermore, caution should be taken in administration of QTc-prolonging medications such as antipsychotics, even if the patient has previously been taking them, as there appears to be acute, transient prolongation of the QTc interval and increased QT variability during alcohol withdrawal. There is currently no recommendation for prophylactic antiarrhythmic therapy or continuing therapy after alcohol withdrawal has subsided.

100.2.2 Cocaine

Vignette *A 44-year-old man presents to the emergency department with complaints of mid-sternal chest discomfort of moderate severity, which has been unremitting for the past 3 hours and radiates to his shoulders. He notes palpitations, feelings of uneasiness, and resting dyspnea. He is a long-standing smoker and has untreated bipolar disorder. He denies illicit drug use but became more agitated when this line of questioning was pursued. Examination reveals an alert male somewhat apprehensive but with normal cognition. Blood pressure is 178/90 mm Hg and pulse rate is 95 beats per minute, while respiratory rate, temperature, and oxygen saturation are within normal limits. Cardiovascular exam reveals normal*

jugular venous pressure and a soft systolic murmur. Lung auscultation is normal. Urine toxicology is positive for benzoylecgonine. ECG demonstrates ST segment elevation in leads V2–V5 with peaked T-waves. QRS duration and rate-corrected QT (QTc) intervals are prolonged. Chest x-ray and serum chemistries (including cardiac troponin) are unremarkable. Upon sharing these results, the patient confides that he and his girlfriend consumed an "eight-ball" (3.5 grams) of cocaine by intranasal route.

Cocaine (benzoylmethylecgonine) is a crystalline alkaloid, derived from the coca plant that is among the most widely abused drugs worldwide. It is a consumed via intranasal insufflation, inhaled vapor from smoking a freebase combination with sodium bicarbonate, or the intravenous route. Cocaine incites a wide array of cardiovascular consequences ranging from acute alterations in hemodynamics to myocardial ischemia, ventricular arrhythmias, and dilated cardiomyopathy (Table 100.1). The extensive effects on the cardiovascular system result from its numerous mechanisms of action. Cocaine is a potent sympathomimetic that augments central sympathetic outflow and has the ability to increase peripheral catecholamine concentration. Cocaine also exhibits antiarrhythmic-like inhibition of voltage-gated sodium channels and potassium channels and has complex, poorly understood interactions with L-type calcium channels (Ramirez et al. 2012).

100.2.2.1 Hemodynamics

Cocaine incites a range of hemodynamic alterations. Sympathomimetic activity dominates at low to moderate doses resulting in tachycardia, systemic vasoconstriction, and coronary vasospasm. However, at higher doses, cocaine's sodium and potassium channel inactivation can lead to cardiodepression, tachy- and bradydysrhythmias, and even vasodilation (Egashira et al. 1991a; Schwartz et al. 2010).

When taken at low doses (~0.35 mg/kg) through the intranasal route, cocaine ingestion simply results in slight elevation of systolic blood pressure, while higher doses (~1.3 mg/kg) will cause an increase in systolic and diastolic blood pressure (~30/15 mmHg) and elevation of the heart rate (~20 bpm). The onset of these alterations occurs at 2 min and peaks at 5–10 min (Resnick et al. 1977). Moderate cocaine doses (2–3 mg/kg) have a positive inotropic effect, resulting in an increase in left ventricular contractility and cardiac index (Boehrer et al. 1992). In sum, low to moderate doses of cocaine result in tachycardia and in hypertension via a rise in both systemic vascular resistance and cardiac output.

The mechanism of catecholamine response is dependent on the route of cocaine administration. Experimentally, intravenous infusion of cocaine in humans blocks the reuptake of catecholamines peripherally, thereby increasing available norepinephrine in the heart and vascular smooth muscle (Muscholl 1961; Tuncel et al. 2002). However, when consumed by the intranasal route, peripheral norepinephrine levels are not elevated (Tuncel et al. 2002). Therefore, the mechanism of hypertension in acute cocaine intoxication following intranasal is due to an increase of central sympathetic outflow (Vongpatanasin et al. 1999).

Tachycardia is mediated through β-adrenergic receptor interactions as nonselective β-blockade with propranolol abolishes the increase in heart rate caused by cocaine (Kenny et al. 1992). Hypertension is partially mediated through α-adrenergic receptors as α-blockade with prazosin experimentally prevents vasoconstriction (Egashira et al. 1991a). However, positive inotropic effects facilitated through β-adrenergic stimulation contribute to hypertension caused by cocaine, as propranolol attenuates the rise in mean arterial pressure by diminishing the cocaine-mediated rise in left ventricular contractility. Combined α- and β-blockade with labetalol eliminates cocaine's chronotropic effect on the heart and significantly blunts the increase in blood pressure (Kenny et al. 1992).

Cocaine use has also been implicated in epicardial coronary artery vasospasm. Animal studies demonstrate that intravenous cocaine administration results in coronary vasoconstriction with a decrease in coronary diameter of 15–46 % (Benzaquen et al. 2001). In addition to α-adrenergic stimulation, cocaine causes vasospasm by increasing the expression of the potent vasoconstrictor endothelin and decreasing levels of nitric oxide (Mo et al. 1998; Wilbert-Lampen et al. 1998). Denuded endothelium that simulates atherosclerotic coronary artery disease exhibits a mean greater degree of narrowing compared to healthy coronary arteries experimentally (Egashira et al. 1991b). Human data have corroborated these observations. In several studies employing a recreational dose of cocaine (2 mg/ml) intranasally in humans, coronary caliber has been shown to decrease (Benzaquen et al. 2001). In a study of patients with and without coronary artery disease undergoing diagnostic catheterization, coronary diameter decreased more than twice as much in diseased arteries (>50 % stenosis) versus normal arteries (Flores et al. 1990). The time course of coronary vasospasm does not simply follow peak serum levels of cocaine. In fact, coronary vasoconstriction was found to occur at a greater magnitude at 90 min post administration when cocaine metabolites were highest compared to 30 min when serum cocaine levels peaked (Brogan et al. 1992). The degree of vasospasm is augmented by concurrent cigarette smoking with 19 % reduction in coronary diameter seen with simultaneous cocaine and smoking and 7 % reduction seen with cocaine alone in one study (Moliterno et al. 1994). The risk of coronary events is further heightened by cocaine's ability to activate platelets and provoke shear stress.

Cocaine infusion has been shown to be directly cardiodepressant in animal models and in vitro human cardiomyocytes (Egashira et al. 1991a; Perreault et al. 1993). This cardiodepression occurs independently of alterations in coronary blood flow (Morcos et al. 1993). The negative inotropic effect of cocaine is paralleled by a decrease in ventricular myocyte intracellular calcium concentration. The mechanism responsible for direct cardiodepression is hypothesized to result from decreased intracellular sodium concentration caused by voltage-gated sodium channel inactivation by cocaine. This results in less sodium available for the sodium-calcium exchanger in the sarcoplasmic reticulum, less calcium storage in the myocytes, and therefore lower intracellular calcium concentrations during depolarization (Perreault et al. 1993). In fact, it has been found that when cocaine's sympathomimetic action on the heart is blocked with β-adrenergic receptor

antagonists, cocaine's direct effect on the heart is unmasked and left ventricular contractility is significantly reduced (Kenny et al. 1992).

100.2.2.2 Myocardial Ischemia

Cocaine is responsible for 57 % of illicit drug-related emergency department visits in the United States, and chest pain is the most common presenting symptom (Finkel and Marhefka 2011). Cocaine-related chest pain is typically described as pressure-like in quality and is frequently associated with dyspnea, diaphoresis, nausea, palpitations, and anxiety (McCord et al. 2008). The reported incidence of acute myocardial infarction (MI) in patients with cocaine-related chest pain ranges between 0.7 % and 6 %. There is a 24-fold increased risk of acute MI within the first hour of cocaine use. However, myocardial injury can also occur hours after use presumably due to cocaine metabolites (Mittleman et al. 1999; McCord et al. 2008). Cocaine is estimated to play a role in one out of four MIs in patients between the ages of 18 and 45, and half of patients with cocaine-related MIs have no evidence of atherosclerotic coronary artery disease on angiography (Lange and Hillis 2001; Qureshi et al. 2001). All routes of administration appear to carry a similar risk of acute MI.

The diagnosis of myocardial infarction in those with recent cocaine use is difficult. There are no historical factors useful for distinguishing MI from chest pain without myocardial injury in this population. Specific characteristics of pain such as onset, location, quality, and duration are not predictive, nor are histories of chest pain, myocardial infarction, or risk factors for atherosclerotic coronary artery disease (Hollander et al. 1994). Furthermore, in the presence of cocaine, electrocardiograms (ECGs) can exhibit abnormal repolarization in the absence of ischemia. Presenting ECGs are abnormal in approximately 55–85 % of cocaine users, and up to 43 % of patients with cocaine-related chest pain meet diagnostic criteria for ST-elevation MI (as defined by >0.1 mV elevation in contiguous leads) (Gitter et al. 1991; Chakko et al. 1994; Hollander et al. 1994). The positive predictive value of ECG for MI in this population is reportedly only 18 % with a sensitivity of approximately 36 % (Hollander et al. 1994). Serum levels of creatinine kinase can be misleading presumably due to rhabdomyolysis (Gitter et al. 1991). However, serum troponin assays remain effective in detecting myocardial injury in cocaine users (Lange and Hillis 2001; Finkel and Marhefka 2011).

Myocardial ischemia is caused by misbalance of oxygen supply and demand. The sympathomimetic actions of cocaine augment myocardial oxygen consumption by increasing heart rate, blood pressure, and myocardial contractility (Lange and Hillis 2001). Simultaneously, coronary artery vasoconstriction, which occurs more dramatically in segments with significant atherosclerosis, decreases oxygen supply. Habitual cocaine use has been linked to premature coronary artery disease in postmortem studies, which is thought to result from increase vascular permeability to LDL and amplified expression of leukocyte adhesion molecules (Lange and Hillis 2001). Acute cocaine use is also associated with intracoronary thrombus formation, which may result from cocaine's ability to activate and trigger aggregation of platelets and augment levels of fibrinogen, von Willebrand factor, and

plasminogen activator inhibitor, without a corresponding increase in plasmin (Heesch et al. 2000; Lange and Hillis 2001; Siegel et al. 2002).

To our knowledge, there have been no randomized, placebo-controlled trials addressing improving outcomes in cocaine-related MIs (McCord et al. 2008). Those with chest pain in the setting of cocaine use should receive IV benzodiazepines as early management, as their use relieves chest pain and mitigates hemodynamic alterations. Nitroglycerin reverses cocaine-associated coronary vasoconstriction and should also been given as a first-line agent. Calcium channel blockers are recommended after benzodiazepines and nitroglycerin have failed. Although they can reverse coronary vasospasm, use of calcium channel blockers in ACS in the absence of cocaine has not been shown to improve survival and may even increase mortality rates in those with decreased left ventricular function. Phentolamine, an α-adrenergic blocker, may also be administered as a second-line agent, as it reverses coronary vasoconstriction.

Recent guidelines for unstable angina and non-ST-elevation MI caution against the use of β-blockers in patients using cocaine, because unopposed α-adrenergic stimulation can potentially exacerbate coronary vasoconstriction and worsen arterial hypertension (McCord et al. 2008; Anderson et al. 2011). β-blockers have been shown to reduce mortality when given orally in the first 24 h in acute coronary syndrome not related to cocaine. However, the mortality rate in cocaine-related MI is lower, which alters the risk/benefit ratio of this intervention (McCord et al. 2008). There have only been two studies that prospectively evaluated the effect of β-blockers on coronary artery vasoconstriction in the setting of cocaine use (Lange et al. 1990; Boehrer et al. 1993; Finkel and Marhefka 2011). These two small studies included only nine to ten patients each and evaluated the effects of only propranolol and labetalol, yet are the basis for the recommendation against β-blockers in cocaine-related chest pain patients (Finkel and Marhefka 2011).

In opposition, recent retrospective studies have evaluated outcomes in patients with cocaine-related chest pain who were given β-blockers prior to the discovery of their recent cocaine use. It was found that β-blocker therapy was associated with a lower incidence of MI without change in the rate of adverse outcomes or peak levels of troponin (Dattilo et al. 2008; Rangel et al. 2010; Ibrahim et al. 2013). In one study, there was a trend toward decreased post-hospital mortality in those receiving β-blockers (Rangel et al. 2010). The 2011 updated AHA guidelines state that it is reasonable to consider administering a combined α- and β-blocker like labetalol in situations when patients are hypertensive and tachycardic and have received a vasodilator such as nitroglycerin or a calcium channel blocker in close temporal proximity (Anderson et al. 2011). Much is still unknown about the potential benefit and harm of β-blockers in patients with cocaine-related myocardial ischemia, and caution should be taken with their use until further investigation has been conducted.

Due to the risk of coronary thrombus formation, patients should be given aspirin, and those with proven MI should receive unfractionated heparin or low molecular weight heparin if there are no contraindications (McCord et al. 2008). Fibrinolytics should be used with caution, as there are reports of devastating complications in

cocaine users, and the diagnosis of STEMI is challenging in this population due to baseline ECG abnormalities (Lange and Hillis 2001; McCord et al. 2008). Percutaneous coronary intervention is the preferred management of intracoronary thrombus, but fibrinolytics can be used in cases of persistent ST segment elevation after nitroglycerin and calcium channel blockers have been given if there are no contraindications and coronary angiography is not available (McCord et al. 2008; Anderson et al. 2011).

Outcomes are generally better in cocaine-related MI compared to MI not related to cocaine (McCord et al. 2008). The incidences of ventricular arrhythmias, congestive heart failure, and death are 4–17 %, 5–7 %, and <2 %, respectively (Lange and Hillis 2001). The better outcomes are presumably due to the overall younger age of patients experiencing MI while using cocaine. However, those who experience cocaine-related MI are at high risk for recurrent ischemic events as more than half will continue to use cocaine and up to 58 % will have recurrence of ischemia (McCord et al. 2008).

100.2.2.3 Cardiac Conduction and Arrhythmia

Cocaine can cause a wide range of electrocardiographic alterations owing to its sympathomimetic actions and antiarrhythmic properties (Ramirez et al. 2012). Cocaine acts similar to class I antiarrhythmic by blocking voltage-gated sodium channels (I_{Na}) in the inactive state. Cocaine also blocks the *hERG*-coded voltage-gated potassium channel responsible for the rapid delayed rectifier potassium current (I_{Kr}) that allows for repolarization. Together, the inhibition of I_{Na} and I_{Kr} slows the rapid upstroke of the action potential during phase 0 and prolongs the action potential duration by delaying phase 3. Electrocardiographically, this results in widening of the QRS complex and prolongation of the QT interval.

Clinically, cocaine use is associated with a variety of arrhythmias (Table 100.2) (Lange and Hillis 2001). The most common alteration is sinus tachycardia, but an assortment of other supraventricular rhythm disturbances has been temporally related to cocaine use, including nonsustained supraventricular tachycardia, atrial fibrillation, and sinus bradycardia (Ramirez et al. 2012). Excluding torsades de pointes, prospective studies on patients consuming cocaine have not consistently demonstrated an increase risk of ventricular arrhythmias other than frequent premature ventricular contractions. However, the literature contains frequent case reports of monomorphic ventricular tachycardia and ventricular fibrillation in cocaine users. These associations are often confounded by polysubstance use and electrolyte derangements, especially acidosis.

A prospective trial demonstrated that when habitual users smoke cocaine, the rate-corrected QT interval (QTc) modestly increases (Magnano et al. 2006). Furthermore, a retrospective report found that QTc interval prolongation is present in approximately 4 % of chronic cocaine abusers, 26 % of patients treated for cocaine toxicity in the ED, and 75 % of cases of cocaine-related mortality (Chakko et al. 1994). In addition to its ability to prolong the QT interval, cocaine has been shown to induce early afterdepolarizations, further increasing the risk of the ventricular arrhythmia torsades de pointes (Kimura et al. 1992). In the case report

Table 100.2 Arrhythmias and ECG abnormalities associated with cocaine

Arrhythmia	ECG abnormality
Sinus tachycardia	PR interval shortening
Sinus bradycardia	PR interval lengthening (first-degree AV block)
Supraventricular tachycardia	
Atrial fibrillation	QRS widening
Atrial flutter	Nonspecific intraventricular block
Second- and third-degree AV block	Right bundle branch block
Accelerated idioventricular rhythm	Left bundle branch block
Torsades de pointes	Left anterior fascicular block
Ventricular tachycardia	QT interval prolongation
Ventricular fibrillation	ST segment elevation/depression
Asystole	T wave peaking, flattening, inversion
	Acquired Brugada syndrome
	ST elevation, down-sloping ST segment, and T wave inversion

literature, QT prolongation is frequently reported, and associated torsades de pointes occurred in almost half of these cases (Ramirez et al. 2012).

Cocaine has seemingly contradictory interactions with atrioventricular conduction (Ramirez et al. 2012). Several small observational studies have shown that cocaine use is associated with PR segment shortening, which would suggest that cocaine enhances conduction through the AV node. However, the case report literature is incongruent with these results and contains several cases of PR prolongation with various degrees of AV block. QRS interval widening reportedly occurs in up to 6 % of patients using cocaine, which is most commonly due to nonspecific intraventricular conduction delay or right bundle branch block. It is important to note that many of these cases may be confounded by electrolyte derangements and concomitant ingestion of other substances.

There have been cases of acquired Brugada pattern associated with cocaine use (Ramirez et al. 2012). However, electrophysiologic testing did not induce sustained ventricular arrhythmias in any of these cases, and it is unknown if cocaine-associated Brugada pattern confers any additional risk of sudden cardiac death.

100.2.2.4 Other Effects: Cardiomyopathy, Endocarditis, Aortic Dissection, and Stroke

Cocaine can cause left ventricular hypertrophy and systolic dysfunction (Lange and Hillis 2001). Administration of cocaine in animal models acutely results in left ventricular dilation and decreased contractility, while intracoronary administration in humans has been shown to be negatively inotropic (Perreault et al. 1993; Schwartz et al. 2010). There are reports of dilated cardiomyopathy in long-term cocaine users as well as acute, reversible, profound left ventricular dysfunction after acute cocaine binge use (Lange and Hillis 2001). Additionally, transient left

ventricular apical ballooning syndrome (takotsubo cardiomyopathy) has been temporally related to acute cocaine intoxication (Schwartz et al. 2010). One study found that left ventricular dysfunction is present in 7 % of apparently healthy, asymptomatic cocaine users (Bertolet et al. 1990).

In those with congestive heart failure, stimulant use (cocaine and amphetamines) is associated with an increased incidence of hospitalization and reduced ejection fraction (Diercks et al. 2008). Cocaine cessation leads to improved cardiac function, and cocaine relapse can cause recurrence of decompensated heart failure (Schwartz et al. 2010). The possible mechanisms of cocaine's effects on myocardial systolic dysfunction include myocardial ischemia/infarction, repetitive sympathetic stimulation of the myocardium (similar to cardiomyopathy associated with pheochromocytoma), hypersensitivity to adulterants or infectious agents leading to myocarditis, alteration of intracellular calcium concentration, and stimulation of cytokine production resulting in remodeling and myocyte necrosis (Lange and Hillis 2001).

As with any substance used by the intravenous route, there is a risk of bacterial endocarditis with IV cocaine use (Lange and Hillis 2001). For unknown reasons, cocaine seems to increase the risk of endocarditis compared to other drugs. Left-sided valves are more frequently involved with cocaine than other IV drugs.

Aortic dissection is well described in the setting of cocaine intoxication (Eagle et al. 2002). The prevalence of cocaine use in aortic dissection has been found to range from 0.5 % in a larger multicenter review to 37 % of aortic dissections at a single inner-city hospital. Cocaine-related aortic dissections primarily affect young, black, hypertensive individuals, and there may be a higher risk with crack cocaine use compared to other routes of administration. The mechanism of cocaine's association with aortic dissection is thought to involve arterial hypertension and tachycardia with a resulting increase in arterial shear stress. Cocaine is associated with decreased aortic elasticity, increased smooth muscle cell apoptosis, and premature atherosclerosis, all of which play a role in increasing dissection risk (Eagle et al. 2002; Finkel and Marhefka 2011).

Cocaine use confers a twofold increase in the risk of ischemic and hemorrhagic stroke (Schwartz et al. 2010). Compared to the general population, former cocaine users experience a higher proportion of subarachnoid hemorrhage, while current cocaine users have higher ratios of both subarachnoid hemorrhage and intracerebral hemorrhage. Subarachnoid hemorrhage most commonly results from rupture of arterial aneurysms, and intracerebral hemorrhagic strokes are thought to result from large spikes in blood pressure. Compared to those not using cocaine, cocaine users with hemorrhagic strokes have worse functional outcomes and increase mortality (Martin-Schild et al. 2010). Overall, cocaine is widely considered the most cardiotoxic among drugs of abuse.

100.2.3 Amphetamines

Amphetamines are a group of drugs that are derived from a β-phenylethylamine core structure, a structure also shared by catecholamines. They cause an increase in

catecholamines concentrations both centrally and peripherally by stimulating their release, blocking their reuptake, and inhibiting their metabolism by monoamine oxidase (Fleckenstein et al. 2007). The degree of peripheral and central sympathetic activation varies between the different types of amphetamines (Kaye et al. 2007). Given their sympathomimetic mechanism of action, it is not surprising that amphetamines share many of the adverse cardiovascular effects associated with cocaine. This section focuses on three commonly abused amphetamines: amphetamine, methamphetamine, and 3,4-methylenedioxymethamphetamine (MDMA).

As would be expected with a sympathomimetic drug, amphetamines cause tachycardia, vasoconstriction, and hypertension (Carvalho et al. 2012). In healthy subjects, oral amphetamine administration results in a dose-dependent increase in both systolic and diastolic blood pressure that peaks in 1–2 h (Mas et al. 1999). There is a biphasic heart rate response; the baroreceptor reflex blunts the initial rise in heart rate, but heart rate quickens again 3–4 h later when blood pressure begins to lower.

The most common clinical presentations of amphetamine users requiring hospitalization are chest pain syndrome, cardiac arrhythmias, palpitations, and hypertension (Kaye et al. 2007). Acute coronary syndrome and acute MI are particular concerns in this population. One series found that 25 % of patients using methamphetamine that presented with chest pain to the emergency department were diagnosed with an acute coronary syndrome (Turnipseed et al. 2003). Indeed, there are an abundance of reports of acute MI in amphetamine users presenting to the ED and in postmortem series (Kaye et al. 2007; Carvalho et al. 2012). Furthermore, patients suffering acute MI associated with amphetamine use are often young. For example, a 15-year-old boy with no previously known cardiac abnormalities had an MI after starting extended-release amphetamine salts for attention deficit disorder (Sylvester and Agarwala 2012). The pathogenesis of cardiac ischemia in the setting of amphetamines results from an increase in myocardial oxygen demand, through augmentation in chronotropy, wall stress, and afterload, with a reduction in coronary blood flow secondary to vasoconstriction (Kaye et al. 2007; Carvalho et al. 2012). The risk of ischemia may be further increased in long-term users, as postmortem and angiographic data suggests that amphetamines may cause premature coronary atherosclerosis (Kaye et al. 2007).

Amphetamines have been associated with sudden cardiac death and ventricular arrhythmias (Bennett and Walker 1952; Kaye et al. 2007; Carvalho et al. 2012). Specifically, in animal models, methamphetamine has been shown to inhibit the channels responsible for the transient outward potassium current, inward rectifying potassium current, and L-type calcium current (Liang et al. 2010). In humans, methamphetamine has been shown to prolong the QTc interval in humans increasing the risk of torsades de pointes (Haning and Goebert 2007).

Aortic dissection has been strongly associated with methamphetamine intoxication in case reports (Kaye et al. 2007). In fact, one autopsy series found that after hypertension, methamphetamine use was the most common risk factor for fatal acute aortic dissection (Swalwell and Davis 1999). The pathogenesis of aortic dissection is proposed to be secondary to hypertension, but methamphetamine may also have a direct degenerative effect on the aortic wall (Kaye et al. 2007).

Amphetamine use is linked to cardiomyopathy in the acute and chronic setting (Kaye et al. 2007; Carvalho et al. 2012). Amphetamine-associated cardiomyopathy is usually manifest as the gradual onset of a dilated cardiomyopathy with systolic dysfunction. In some cases, the cardiomyopathy may reverse with abstinence. Additionally, takotsubo cardiomyopathy has been described in the setting of acute amphetamine use (Carvalho et al. 2012). The pathogenesis of cardiomyopathy in these patients is probably multifactorial with contributions from catecholamine-induced toxicity, oxidative stress, and ischemia (Kaye et al. 2007; Carvalho et al. 2012). As with other cardiomyopathies, the cornerstone of therapy is neurohormonal blockade with β-blockers, renin-angiotensin-aldosterone system blockade with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and/or aldosterone antagonists, and possibly vasodilators including long-acting nitrates and hydralazine. β-blockers are not recommended for use in the setting of acute cocaine intoxication, and the safety of their long-term use in patients who continue to use sympathomimetic recreational drugs is unknown. Because of the lack of prospective data, β-blocker therapy may be considered only after careful risk-benefit assessment and ideally after documentation of sustained abstinence (Schwartz et al. 2010). Where available, ivabradine may be an alternative to β-blockers in the setting of ongoing cocaine or amphetamine abuse, as it lowers the heart rate and has been shown to improve outcomes via mechanism unrelated to the adrenergic receptor (van Bilsen et al. 2009).

100.2.4 Opioids

Opioids exert their principal clinical actions of analgesia and euphoria via agonist activity at the μ-opioid receptor in the central nervous system (CNS). Respiratory depression occurs in a dose-dependent manner and represents the principle cause of opioid-related mortality. By contrast, cardiovascular effects tend to be relatively mild, with no direct effect of most opioids on cardiac rhythm or myocardial contractility. However, orthostatic hypotension may occur, presumably secondary to histamine release and vasodilation of peripheral arteriolar vessels. In patients with acute coronary syndromes, opioids are often used intravenously for relief of chest discomfort. Intravenous morphine is most frequently utilized in acute myocardial infarction. It leads to mild venodilatation, which decreases preload and myocardial oxygen consumption in the setting of left ventricular systolic dysfunction and pulmonary edema. Intravenous opioids also result in a small decrease in pulse and blood pressure in the acute coronary syndrome patient. Opioids may also improve myocardial energetics at the cellular level and have been associated with enhancement of "ischemic preconditioning." This phenomenon entails repetitive episodes of noncritical ischemia, which may provide myocardial protection to patients chronically treated with opioids. In support of this theory, an autopsy study evaluated age and gender matched decedents stratified by the presence of opioid detected at autopsy (Marmor et al. 2004).

The authors found a lower burden of coronary artery disease among opioid users and postulated that this may relate to ischemic preconditioning.

By contrast to the potential protective effects of opioids with regard to atherosclerotic coronary artery disease, more recent evidence suggests that synthetic opioids may adversely influence cardiomyocyte electrophysiology and occasionally lead to malignant arrhythmia. Specifically, synthetic opioids may block the delayed rectifier potassium ion current known as I_{Kr}, which is encoded by the *hERG* gene. This blockade may lead prolongation of the QTc interval in vivo, which is the requisite substrate for drug-induced torsades de pointes, a type of polymorphic ventricular tachycardia (Fig. 100.1).

Vignette *A 34-year-old law school student presents to your psychiatry office with complaints of fevers, malaise, occasional rigors, and fatigue for 10 days. He has been previously treated for major depression but takes no prescription drugs. He has a 7-year history of intermittent recreational opioid abuse. Over the past 6 months he reports escalation in abuse of prescription opioids including oxycodone and hydrocodone cough syrup with dextromethorphan. When he is unable to use opioids, he develops withdrawal symptoms, and 2 weeks ago he admits to a period of intravenous, black-tar, heroin use. His last opioid consumption was 2 hours ago. The patient is in no acute distress. Examination is notable for a temperature of 38.5 degrees Celsius. Blood pressure is 135/70 mm Hg, and pulse is 112 beats per minute. Cardiovascular exam is notable for a grade III systolic murmur at the lower left sternal border accentuated following inspiration. He reluctantly rolled up his sleeves, revealing the presence of healed track marks and a small abscess in the left antecubital fossa. The remainder of his examination is normal.*

100.2.4.1 Heroin

Diacetylmorphine or heroin was originally formulated as an antitussive agent. It is derived from the opium poppy and was extensively marketed by Bayer Corporation before its addictive potential was recognized in the early 1900s (Marmor et al. 2004). Heroin is often injected after heating a liquid solution but increasingly is smoked or nasally insufflated. Like all opioids, its principal medical complication is central nervous system (CNS) depression and respiratory depression.

The effects of heroin on the cardiovascular system are not extensive, which may in part reflect its close derivation from the natural opium poppy. Heroin abuse is associated with acute pulmonary edema, but this is generally non-cardiogenic in origin. The typical hemodynamic findings include normal pulmonary-capillary pressure and a normal or increase cardiac output (Barceloux 2012), suggesting the absence of direct myocardial toxicity. Although moderately elevated pulmonary artery pressures have been described, this is most likely due to direct pulmonary toxicity in the setting of injected impurities or in overdose with hypoxemia leading to subsequent increased pulmonary-capillary leakage.

The most feared cardiovascular complication of heroin abuse is the development of infective endocarditis. Infective endocarditis is diagnosed using the Duke criteria based on a combination of major (bacteremia and valvular vegetation seen on echocardiography) and minor diagnostic criteria including fever, intravenous drug use history, and vascular embolic findings such as nail bed or "splinter" hemorrhages (Durack et al. 1994). Heroin may also result in embolic stroke due to systemic embolization of cardiac valvular vegetations to the brain. Infective endocarditis of the right-sided heart valves (tricuspid and pulmonic) should always alert the clinician to the possibility of surreptitious intravenous drug abuse. Moreover, the type of bacterium isolated from blood cultures may be pathognomonic for intravenous drug abuse. Pyogenic species such as *Staphylococcus aureus* are commonly isolated as this bacterium may be carried on the skin of intravenous drug abusers. In addition, Pseudomonas and even fungal organisms have been reported given the potential for suspending heroin in contaminated water. In suspected cases of endocarditis, a complete skin examination is mandatory that includes the neck, groin, and feet, as patients are not always forthcoming in exposing pathognomonic skin lesions associated with injection drug use. Careful cardiac auscultation is essential, and both systolic (tricuspid and mitral valve destruction) and diastolic (aortic and pulmonic valve destruction) regurgitant murmurs may be detected. Cases of potential endocarditis should be confirmed immediately by transthoracic echocardiography, which is often diagnostic particularly for right-sided valvular vegetation. If there is a high clinical suspicion for this disorder, transesophageal echocardiography is increasingly utilized as it offers enhanced visualization, particularly of left-sided valvular structure.

Since the early 1970s, a high incidence of sudden death has been noted among heroin users, some of whom were receiving methadone treatment. One study suggested that QTc interval prolongation occurred more often among individuals receiving methadone (Lipski et al. 1973). However, this study was not designed to prospectively address the effects of methadone, heroin, or both medications on cardiac repolarization. More recently, in a study of 115 active heroin users admitted to an opioid treatment center, the median QTc interval was not significantly different compared with 57 healthy controls (Lysenko et al. 2008), which suggests that heroin is unlikely to be directly associated with cardiac arrhythmia. This clinical finding is consistent with its pharmacologic classification as a natural (esterified morphine), rather than a synthetic, opioid.

Vignette (Continued) *The patient is effectively treated for tricuspid valve endocarditis with 6 weeks of intravenous antibiotics with resolution of symptoms. He returns to school but eventually begins to relapse and abuse heroin. He asks for assistance and it's decided to induce him onto methadone maintenance therapy. It is initiated on 30mg/day and up-titrated to 90 mg daily at which point he feels well and discontinues illicit opioids entirely. One month later he is at the opioid treatment center in a group counseling sessions and develops the sudden onset of tonic-clonic seizures and loss of consciousness. He regains awareness and is referred for neurologic evaluation. Computed tomography of the brain is normal.*

Subsequently, magnetic resonance imaging is performed without focal lesion and an electroencephalography study is similarly unremarkable. He started on low dose anti-epileptic therapy but one month later is involved in a motor vehicle accident after passing out while driving.

100.2.4.2 Methadone and Synthetic Opioids Used in Addiction Treatment

Methadone is the most commonly utilized medication for treating heroin addiction worldwide given its low cost and long terminal elimination half-life. This allows patients to break the cycle of frequent, daily heroin use. Methadone is a synthetic diphenylpropylamine compound with a chemical structure similar to propoxyphene (Marmor et al. 2004). Propoxyphene was recently removed from the market in the United States and a number of other countries due to reports of QTc interval prolongation and ventricular arrhythmias (Food et al. 2011).

To investigate the effect of synthetic opioids on arrhythmia risk, the principal focus is on cardiac repolarization. Repolarization describes the phase in the cardiac cycle where myocytes "reset" and is clinically characterized by the QTc interval on the surface electrocardiogram. Opioids have generally been considered devoid of cardiac activity. However, the cardiac repolarization changes associated with synthetic opioids were characterized in human cells stably transfected with the hERG gene which encodes the I_{Kr} current (Katchman et al. 2002). The ratio of the concentration of drug that blocks 50 % of I_{Kr} channels (IC50%) was divided by the expected maximal plasma concentration (Cmax) in man for the individual drugs yielding the IC50/Cmax. This ratio predicts the likely occurrence of QTc prolongation, with higher numbers suggesting the greatest margin of safety. The IC50/Cmax observed with codeine and morphine (and by extension diacetylmorphine or heroin) was >400 uM. These "naturally occurring" opioids therefore are not associated with QTc prolongation and torsades de pointes. By contrast, the synthetic opioids fentanyl, meperidine, and buprenorphine exhibited modest blockade with IC50/Cmax ranging from approximately 50 to 200. Notably, the most potent I_{Kr}-blockade was observed with methadone and levacetylmethadol (LAAM), with ratios of 2.7 and 2.2, respectively. This creates a challenging paradox: while synthetic opioids clearly reduce the harm of injection drug use including the risk of hepatitis, HIV infection, and endocarditis, they also have a cardiac safety liability in susceptible individuals.

From a clinical perspective, LAAM was first shown to have a dose-dependent relationship with cardiac repolarization in 2001 (Huber et al. 2001). LAAM, a long-acting methadone derivative was discontinued from the market in Europe, Australia, and the United states in 2003 due to its association with cardiac arrhythmia. This leaves methadone and sublingual buprenorphine as the primary therapeutic choices for opioid-dependent patients. In 2002, a case series of torsades de pointes associated with high-dose oral methadone was first described (Krantz et al. 2002). In the case presented within the clinical vignette, it is likely that the patient's grand mal seizures and syncope were manifestations of torsades de pointes. Torsades de pointes is a self-terminating arrhythmia in most cases, though it may degenerate

into ventricular fibrillation and lead to sudden cardiac death. A case of methadone-induced arrhythmia masquerading as epilepsy has been previously described (Krantz et al. 2005). This highlights the fact that ventricular arrhythmia if prolonged may result in marked reduction of cardiac output and cerebral hypoxemia and subsequent seizures. Thus, seizures are not always due to epilepsy and should alert clinicians to the possibility of life-threatening arrhythmia.

Many addiction clinicians are unaware of the cardiac arrhythmic properties of synthetic opioids used in treating opioid dependency (Krantz et al. 2007). However, a recent registry study found that ventricular arrhythmia and cardiac arrest are now the most frequent FDA-reported class of methadone-associated adverse events, and reports of QTc prolongation and torsades de pointes have increased sharply in the past decade (Kao et al. 2013). In this study, methadone was associated with a disproportionate signal of torsades de pointes reporting similar to that of drugs with established proarrhythmic properties (such as dofetilide). By contrast, propoxyphene, which was recently withdrawn from the market due to QTc prolongation and dysrhythmia, was not associated with disproportional arrhythmia reporting. Because available evidence definitely suggests that both oral and intravenous methadone hydrochloride cause QTc interval prolongation and torsades de pointes, a consensus guideline suggesting QTc interval screening was developed (Krantz et al. 2009). The guideline emphasized five recommendations for physicians prescribing methadone (Table 100.3). Because the arrhythmia risk associated with methadone is a direct consequence of its effect on cardiac repolarization, the recommendations are applicable to patients either receiving current treatment with methadone or being considered for initiation of methadone treatment for addiction or pain management. Because methadone is now considered an essential medication by the World Health Organization, its utilization is expected to rise, highlighting the need to enhance its cardiac safety.

Table 100.3 Consensus recommendations for QTc interval screening in methadone treatment (Krantz et al. 2009)

Recommendation 1 (disclosure)	Clinicians should inform patients of arrhythmia risk when they prescribe methadone
Recommendation 2 (clinical history)	Clinicians should ask patients about any history of structural heart disease, arrhythmia, and syncope
Recommendation 3 (screening)	Obtain a pretreatment ECG for all patients to measure the QTc interval and then a follow-up ECG within 30 days and annually. Additional ECG is recommended if the methadone dosage exceeds 100 mg/d or if patients have unexplained syncope or seizures
Recommendation 4 (risk stratification)	If QTc interval is >450 ms but <500 ms, discuss potential risks and benefits with patients and monitor them more frequently. If the QTc interval exceeds 500 ms, consider discontinuing methadone or reducing the methadone dose; eliminating contributing factors, such as drugs that promote hypokalemia; or using an alternative therapy
Recommendation 5 (drug interactions)	Clinicians should be aware of interactions between methadone and other drugs that possess QT interval-prolonging properties or slow the elimination of methadone

100.2.5 Nicotine

Cigarette smoking is the leading risk factor for developing cardiovascular disease, increasing risk of coronary artery disease by up to 80–100 % (Law et al. 1997). Secondhand smoke exposure is also harmful, potentially increasing risk of coronary artery disease by up to 30 % (Whincup et al. 2004). Furthermore, pipe smoking, smokeless tobacco, and cigars are all associated with increases in cardiovascular morbidity and mortality (Katsiki et al. 2013). Nicotine is the addictive and primary active component in tobacco products and causes many of the adverse cardiovascular effects of smoking. Nicotine acts in part by stimulating release of norepinephrine from sympathetic nerves and by release of epinephrine from the adrenal glands, which produce increases in heart rate and blood pressure shortly after exposure. Although the precise role of nicotine relative to other components of cigarette smoke is unclear, cigarette smoking is also associated with vasomotor dysfunction mediated by reduced availability of nitric oxide, systemic inflammation that increases adherence of leukocytes to endothelial cells, increases in serum low-density lipoprotein and triglycerides with decreases in high-density lipoprotein, platelet dysfunction, and alteration of thrombotic factors (Ambrose and Barua 2004). Consequently, cigarette smoking is associated with increased rates of all-cause and cardiovascular mortality, first myocardial infarction, recurrent infarction or revascularization in patients with coronary artery disease, sudden death, and stroke (Foody et al. 2001; Prescott et al. 2002; Rodriguez et al. 2002; Goldenberg et al. 2003).

Cessation of smoking is associated with rapid decreases in cardiovascular events including myocardial infarction, stroke, and sudden death, with rates returning to near that of nonsmokers within 3–4 years in many cases (Rea et al. 2002; Gellert et al. 2013). Although the increased risk of cardiovascular events associated with smoking appears to increase with age, the benefits of cessation are independent of age. Despite the clear risks of smoking and benefits of smoking cessation, smoking rates remain relatively stable, and the rate at which physicians in the United States advise patients to stop smoking has actually decreased over the last 10 years (Kruger et al. 2012). Intensive support including structured behavioral modification counseling and pharmacotherapy with either nicotine replacement therapy and/or bupropion appears superior to one-time counseling in patients hospitalized for coronary disease or heart failure, although even a brief statement to outpatients of the risks associated with smoking can result in increases in smoking cessation (Lin et al. 2013).

The acute hemodynamic effects of nicotine withdrawal are poorly characterized, but appear minimal. Blood pressure and heart rate are likely to decrease compared with ongoing tobacco use (Morrell et al. 2008), and withdrawal symptoms are primarily limited to psychosocial changes including prominent irritability. Consequently, abrupt smoking cessation as may occur during hospitalization for myocardial infarction or heart failure is unlikely to adversely affect an individual's hemodynamic status. Theoretical concerns regarding vasoconstrictor activity of nicotine and rare anecdotal reports of myocardial infarction in patients

taking nicotine replacement therapy, particularly those who continue to smoke, have resulted in caution in using nicotine replacement therapy in patients with known coronary artery disease, including immediately post-myocardial infarction (Hubbard et al. 2005; Woolf et al. 2012). However, large studies have failed to show an increased risk of cardiovascular events or death following initiation of nicotine replacement therapy in the setting of cardiovascular disease. Furthermore, effects of continued smoking on platelet activation, hypercoagulability, and other factors suggest that any small increase in atheroembolic risk associated with nicotine replacement therapy is far outweighed by the potential benefits of smoking cessation. There are very few drug-drug interactions between nicotine replacement therapy and cardiovascular medications. Bupropion appears safe to use in patients hospitalized for acute myocardial infarction, but may not be as effective as in chronic, stable outpatients (Eisenberg et al. 2013). Varenicline has not been studied specifically in the acute post-myocardial infarction setting. The use of varenicline in patients with cardiovascular disease is controversial due to some evidence of trends toward a small increase in cardiovascular events in unselected populations (Ware et al. 2013), and the FDA issued an advisory in 2011 that varenicline may increase the risk of adverse cardiovascular events in patients with known cardiovascular disease (US Food and Drug Administration 2011). However, these findings have not been verified, and it is likely that any increased risk is quite small (Prochaska and Hilton 2012). Nonetheless, given the paucity of safety data with varenicline in patients with known cardiovascular disease, patients using varenicline should seek medical attention promptly if their cardiovascular symptoms worsen.

The effects of smoking ordinances that reduce secondhand smoke exposure and the risk of myocardial infarction are an important albeit controversial international public health issue. The biologic effects of secondhand smoke have been well characterized and mirror those of direct tobacco exposure. In particular, coronary arterial plaque destabilization is triggered by nicotine in secondhand smoke; this stimulates the matrix metalloproteinase enzyme that degrades the fibrous cap in coronary plaques (Carty et al. 1996). Secondhand smoke is also associated with impaired coronary endothelial function, increased aortic stiffness (Mahmud and Feely 2003), as well as reduced heart rate variability (15), a marker of abnormal sympathetic nervous system activity. Early studies examining the effect of smoking ordinances found unexpectedly large reductions in myocardial infarction as high as 40 % in Helena, Montana, United States (Meyers et al. 2009). Larger statewide and countrywide smoking studies have been completed including Scotland, England, Italy, the Netherlands, New Zealand, Ireland, and the United States, suggesting an attenuated impact from smoking legislation. In particular, one US analysis found that in contrast to smaller regional studies, smoking bans were not associated with statistically significant short-term declines in mortality or hospital admissions for myocardial infarction or other diseases (Shetty et al. 2010). Regardless of the ultimate impact of smoke-free policy on cardiovascular events, it remains clear that nicotine is among the most highly active substance in tobacco leading to adverse cardiac physiology.

100.2.6 Cannabis

Cannabis (marijuana) is generally thought to be relatively benign by the community despite growing evidence that implicates it in several serious cardiovascular complications including myocardial infarction and ischemic stroke (Bachs and Morland 2001). Cannabis is most commonly smoked and rapidly absorbed through the lungs with physiologic changes appearing shortly after use (Ghuran and Nolan 2000). When consumed through the enteral route, absorption is slower and less predictable. The primary active constituent of cannabis is Δ-9-tetrahydrocannabinol (THC), which interacts with G-protein-coupled cannabinoid receptors (CB1 and CB2) (Pertwee 2006). CB1 receptors are found primarily on neuronal tissue, and their activation at peripheral nerve terminals inhibits neurotransmitter release (Pertwee 2006). In addition, there may be cross talk between CB1 and α_2-adrenergic receptors on the presynaptic autonomic nerves.

THC causes a biphasic autonomic response. The sympathetic nervous system is activated at low to moderate doses and the parasympathetic nervous system predominates at higher doses (Ghuran and Nolan 2000). This results in tachycardia and augmented cardiac output at lower doses and hypotension and bradycardia at high doses. Even at low doses, cannabis can cause both hypertension and hypotension. Blood pressure alterations during cannabis use are often positional; blood pressure increases while in the seated or supine position and drops while standing (Pratap and Korniyenko 2012). Hypotension can also occur during the act of smoking due to rapid changes in autonomic nervous system output, and orthostatic hypotension with resulting syncope is not an uncommon occurrence. Autonomic changes are generally well tolerated in healthy individuals, and cannabis-induced hypotension usually resolves spontaneously or responds to intravenous fluid boluses (Ghuran and Nolan 2000).

Cannabis use increases myocardial oxygen demand by increasing heart rate, wall stress, and sometimes blood pressure. Additionally, when smoked, it decreases oxygen supply through carboxyhemoglobin formation (Aronow and Cassidy 1974). Cannabis use has been shown to decrease threshold to symptomatic angina pectoris. Furthermore, one study demonstrated that the risk of acute MI is 4.8 times higher within the hour following cannabis use (Mittleman et al. 2001). A follow-up study of these MI patients found that continued marijuana use of more than once per week was associated with a 4.2-fold increased risk of death over a 3.8-year period (Mukamal et al. 2008).

In addition to cardiac ischemia, evidence is emerging that implicates cannabis use with inciting ischemic stroke (Wolff et al. 2013). As of 2013, there have been 59 reported cases of stroke associated with cannabis use. All but one were ischemic in origin and the patients were often young. Cannabis use has been particularly strongly associated with two specific etiologies of ischemic stroke: reversible cerebral vasoconstriction syndrome (RCVS) and multifocal intracranial stenosis (MIS). In a prospective study evaluating cannabis' role in ischemic stroke, a single center enrolled every patient under 45 years of age that presented with ischemic stroke (Wolff et al. 2011). It was found that cannabis use was highly associated with

ischemic strokes caused by multifocal intracranial stenosis. In this study, ten of 11 multifocal intracranial stenosis stroke patients had used cannabis for years, and all had binge-smoked cannabis the day prior to their ischemic events. Caution must be taken with attributing these events solely to cannabis, as all patients also smoked tobacco regularly and half of these patients had binged on alcohol shortly before their ischemic events.

Epidemiological data demonstrates that cannabis users are more likely to feel palpitations than nonusers, which is usually caused by sinus tachycardia (Petronis and Anthony 1989). However, other arrhythmias have also been temporally related to cannabis use such as sinus bradycardia, atrial fibrillation, atrial flutter, ventricular extrasystoles, and second-degree AV block (Fisher et al. 2005; Pratap and Korniyenko 2012). The onset of arrhythmias can begin within a few minutes of cannabis use, peaks at about 30 min, and can last as long as 90 min (Johnson and Domino 1971). The majority of these arrhythmias revert spontaneously to sinus rhythm. If persistent, the American Heart Association and European Society of Cardiology management protocols should be followed (Fisher et al. 2005). There are two cases of cannabis-induced Brugada pattern, neither of which were associated ventricular arrhythmias (Pratap and Korniyenko 2012). Although reports of ventricular arrhythmias are not common with cannabis use, a postmortem case series carried out on six patients with unexplained sudden death with recent cannabis use concluded that causes of death were "acute cardiovascular events," possibly representing fatal arrhythmias (Bachs and Morland 2001).

100.3 Anabolic Steroids

Anabolic steroids have varying degrees of androgenic properties and are frequently utilized by athletes, weightlifters, and bodybuilders to enhance athletic performance and strength. Anabolic steroids are associated with direct effects such as left ventricular hypertrophy and myocardial fibrosis and indirect effects, including dyslipidemia, hypertension, arrhythmia, and myocardial infarction (Higgins et al. 2012). It is likely that chronic exposure to these agents can result in significant alterations in the cardiovascular system, beyond the expected increase in salt and water retention leading to elevations in blood pressure in susceptible patients.

Cardiomyocytes have testosterone receptors, which may explain the propensity to muscular hypertrophy in the setting of supraphysiologic doses. The most feared complication of anabolic steroids, however, is the increased risk of ischemic cardiovascular events. Numerous reports of myocardial infarction have been described in the literature even among young patients. In addition, there is further concern that anabolic steroids may accelerate the overall atherosclerotic process with ongoing abuse. A framework for understanding this risk has been put forward (Melchert and Welder 1995). Four mechanisms are suggested: (1) atherosclerosis-dyslipidemia model given marked reductions up to 70 % in high-density lipoprotein (HDL) cholesterol, which is responsible for reverse cholesterol transport and >20 % increases in the atherogenic low-density lipoprotein (LDL) cholesterol;

(2) vasospasm model given alterations in the vascular nitric oxide system; (3) thrombosis model involving alterations in platelet and clotting function including increases in plasminogen activator activity; and (4) direct myocardial injury model including impaired myocardial relaxation and diastolic dysfunction. Another factor that enhances the risk of myocardial infarction is polycythemia associated with anabolic steroids. This increases blood viscosity and the risk of thrombosis. As such, a complete blood count should be obtained in patients using anabolic steroids who present with ischemic complications. Beyond the risk of acute myocardial infarction, these agents have been associated with cerebrovascular accident (Garcia-Esperon et al. 2013), suggesting that atheroembolic complications may affect all vascular territories. Furthermore, anabolic steroid use has been associated with supraventricular and ventricular ectopy, atrial fibrillation, ventricular fibrillation, and ventricular tachycardia, and cardiac pathology has been frequently observed in deceased anabolic steroid abusers (Thiblin et al. 2000).

Anabolic steroid use should be considered in young athletes with evidence of hypertension, very low serum HDL and elevated LDL cholesterol levels, atrial or ventricular arrhythmias, and/or left ventricular hypertrophy by electrocardiogram or echocardiogram. There is little data regarding cardiovascular risk reduction associated with anabolic steroid use apart from abstinence. The actual prevalence of significant coronary artery disease among anabolic steroid users is not known, and cardiovascular risk reduction should conform to standard age-appropriate guidelines until additional data is available. Blood pressure and lipid abnormalities will generally resolve after 6–12 months of abstinence, but there is evidence that pathologic left ventricular hypertrophy may persist for years after discontinuation of steroid use, although this persistence may be due to sustained or ongoing strength training (Achar et al. 2010). If blood pressure abnormalities are particularly severe, or do not resolve with abstinence, pharmacologic intervention should be considered. Statin therapy should be initiated for sustained LDL cholesterol levels $\geq$160 mg/dL in accordance with current guidelines. Rosuvastatin in particular appears more effective in raising HDL levels than other statins. Omega-3 fatty acids and niacin have also been associated with increases in HDL cholesterol, but their efficacy in reducing risk of cardiovascular effects is uncertain. Antihypertensive therapy should be considered if the blood pressure is consistently $\geq$140/90 in accordance with currently guidelines. The optimal antihypertensive agent for steroid-associated hypertension is unclear, although the stimulation of the renin-angiotensin-aldosterone system observed in anabolic steroid users suggests that ACE inhibitors or angiotensin receptor blockers may be particularly effective and are often tolerated well by young patients. β-blockers are typically not used as monotherapy for hypertension, but may be considered if coexisting arrhythmias are present. There is currently no evidence or recommendation for antiplatelet therapy for primary prevention in anabolic steroid use. There is no clear evidence for pharmacologic treatment of LV hypertrophy, although dilated cardiomyopathy as a result prolonged steroid use and/or ischemic events should be treated in accordance with heart failure guidelines using neurohormonal blockade with β-blockers and renin-angiotensin-aldosterone system inhibitors along with vasodilators and/or diuretics according to patient symptoms.

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Gastrointestinal Disorders Related to Alcohol and Other Drug Use

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Abstract

Acute and chronic gastrointestinal manifestations are common in the setting of alcohol, tobacco, prescription, and recreational drug use. Excessive alcohol use is associated with injury to all parts of the gastrointestinal tract. Within the gastrointestinal tract, alcoholic liver disease, alcoholic pancreatitis, and gastrointestinal cancer are important causes of morbidity and mortality related to excessive alcohol use. Tobacco use is associated with gastroesophageal reflux, peptic ulceration, and gastrointestinal cancer but appears to protect against ulcerative colitis. Opioids have important effects on gastrointestinal secretion and motility. Narcotic bowel syndrome may develop in the setting of escalating doses of opioid analgesia. Cannabinoid hyperemesis syndrome should be considered in the setting of heavy cannabis use and recurrent vomiting. The body packing syndrome is rare but challenging when encountered.

101.1 Introduction

This chapter describes gastrointestinal effects of gastrointestinal disorders secondary to the effects of alcohol, tobacco, prescription, and recreational drugs.

Excessive alcohol use is associated with injury to all parts of the gastrointestinal tract. Several detailed reviews have been published (Bujanda 2000). The gastric mucosa is a target for alcohol-related toxicity but also contributes to the oxidation of alcohol. Within the gastrointestinal tract, liver disease and pancreatitis are important causes of morbidity and mortality related to excessive alcohol use. Symptoms of intestinal dysfunction are common among people with alcohol dependence and include diarrhea and malabsorption.

Tobacco use is associated with gastroesophageal reflux, peptic ulceration, and gastrointestinal malignancy but appears to protect against ulcerative colitis. Opiates have important effects on gastrointestinal secretion and motility. Other drugs of abuse such as cannabis and cocaine uncommonly affect the gastrointestinal tract. The body packing syndrome is rare but challenging when encountered.

101.2 Alcohol

The relative risk of alcohol-related GI toxicity appears to differ between affected tissues and between benign and neoplastic disorders. Similarly the pattern and type of beverage have not been consistently shown to predispose to any specific GI effects of alcohol.

101.2.1 Parotid Glands and Oral Cavity

Painless symmetrical enlargement of the parotid glands (termed sialosis or sialadenosis) is common in patients with alcoholic liver injury (Proctor and Shori 1996). Abelson et al. (1976) found 61 % of patients with alcohol cirrhosis had

enlarged parotid glands. Sialosis is characterized by the triad of acinar cell hypertrophy, myoepithelial degeneration, and neural degeneration. Salivary secretion is reduced in experimental animals given alcohol. These effects may contribute to progressive dental caries and poor oral mucosal health. The effect of alcohol abuse on salivary function in humans is controversial with reports of increased, unaltered (Silver et al. 1986), and decreased salivary flow (Proctor and Shori 1996). Moreover, alcoholics may suffer from inflammation of the tongue (i.e., glossitis) and the mouth (i.e., stomatitis). It is unclear, however, whether these changes result from poor nutrition or reflect a direct effect of alcohol on the mucosa.

101.2.2 Esophagus

Both acute and chronic alcohol consumption are associated with symptomatic gastroesophageal reflux disease (GERD). Dysfunction of the lower esophageal sphincter (LES) and esophageal peristalsis and abnormal gastric acid secretion may be involved in the pathogenesis of alcohol-related GERD. Exposure of the esophagus and stomach to alcohol may cause direct damage to esophageal and gastric mucosa. In addition, acetaldehyde generated from alcohol may affect the function of the esophagus and stomach. Systemic investigations concerning this matter are still inadequate and further well-designed prospective studies are needed to clarify the effect of alcohol on GERD. An Irish study concluded that alcohol consumption in early adulthood may lead to the development of reflux esophagitis. More recent alcohol consumption does not appear to confer any increased risk of reflux esophagitis, Barrett's esophagus, or esophageal adenocarcinoma. In fact, wine consumption may reduce the risk of these esophageal disorders (Anderson et al. 2009).

Reflux episodes were increased by 60 g of ethanol given with a meal to healthy subjects without alcohol dependence (Kaufman and Kaye 1978). These episodes were measured by measurement of esophageal pH for three hours after a standard meal and most were asymptomatic. A number of mechanisms have been identified that may contribute to these effects of alcohol (Lieber 1992b). Direct application of 30 % ethanol, but not lower concentrations, causes injury to the esophageal mucosa. An acute dose of alcohol reduces lower esophageal sphincter pressure (LESP) (Hogan et al. 1972) and reduced maximal LESP stimulated by a meal (Mayer et al. 1978). Chronic excessive alcohol use is also associated with manometric abnormalities relevant to GERD that recover with a month of abstinence (Keshavarzian et al. 1987; Silver et al. 1986). These abnormalities were found regardless of the presence or absence of peripheral neuropathy. These studies provide evidence to support the time-honored advice to reduce alcohol consumption in the presence of symptomatic GERD.

Upper gastrointestinal bleeding (UGIB) is more frequent in alcoholics, especially those with cirrhosis. In a 2007 UK audit of 6,750 patients with acute UGIB, 9 % had known cirrhosis and 26 % a history of alcohol excess (Hearnshaw et al. 2011). A Czech prospective study of 137 cirrhotic patients presenting with acute UGIB found the following causes: esophageal varices (57.7 %), peptic gastric and duodenal ulcers (18.2 %), portal hypertension gastropathy (9.5 %), gastric

varices (5.1 %), reflux esophagitis (2.9 %), Mallory–Weiss syndrome (2.9 %), and erosive gastropathy (1.5 %). The mortality in all bleeding cirrhotic patients was 14.6 % (Svoboda et al. 2012). Mallory–Weiss syndrome is characterized by massive bleeding caused by tears in the mucosa at the cardio-esophageal junction after vomiting. The syndrome accounts for 5–15 % of all cases of bleeding in the upper GI tract. Mallory–Weiss syndrome prevalence varies; it is uncommon in China (Yin et al. 2012). In one series, almost 50 % of these patients, the disorder was caused by increased gastric pressure resulting from repeated retching and vomiting following excessive acute alcohol consumption (Kortas et al. 2001).

101.2.3 Stomach

101.2.3.1 Alcoholic Gastritis

The clinical term "alcoholic gastritis" is nonspecific and is often used to refer to a broad range of upper gastrointestinal symptoms experienced by people who drink alcohol excessively. It has been surprisingly controversial despite considerable study (Feinman et al. 1992; Konturek et al. 1996). The term gastritis is used to denote inflammation associated with mucosal injury. Epithelial cell damage and regeneration without associated inflammation are referred to as "gastropathy" (Dixon et al. 1996). It is often difficult to establish with certainty that a particular agent, such as alcohol, has caused gastropathy. Exposure of the gastric mucosa to 20 % alcohol induces gastric mucosal injury. Lower concentrations are not toxic, whereas higher concentrations lead to extensive hemorrhagic injury (Konturek et al. 1996).

101.2.3.2 Dyspepsia and Ulcer

In humans admitted for treatment of alcohol dependence, gastric hemorrhagic and erosive lesions and ulcers were commonly seen (Segawa et al. 1987). Interestingly, Brown et al. (1981) found that gastritis was not more common in patients with cirrhosis than healthy controls. Gastritis in people with alcohol dependence is strongly associated with *H. pylori* infection, with histological and symptomatic relief after eradication of the organism but no improvement with abstinence from alcohol (Uppal et al. 1991). This finding has been confirmed by another group (Hauge et al. 1994). The presence of alcohol dehydrogenase (ADH) activity in *H. pylori* organisms may tend to protect the alcohol drinking host from infection as exposure to alcohol leads to generation of acetaldehyde that may be bactericidal. Alcohol abuse is associated with reduced medication compliance and delayed healing (Reynolds 1989), but healing of established ulcers is not retarded by moderate alcohol consumption (Battaglia et al. 1990). The available evidence does not convincingly support the conclusion that alcoholic beverages cause chronic chemical gastropathy (Cheli et al. 1981). Moreover, there does not appear to be a link between chronic atrophic gastritis and alcohol consumption (Adamu et al. 2011) and indeed the risk was reduced among moderate drinkers in Germany (Gao et al. 2009).

Other causes may be account for gastritis-like symptoms. Fatty liver may cause upper abdominal discomfort and nausea. It has been proposed that alcohol may

directly induce vomiting by central stimulation of the chemoreceptor trigger zone in the area postrema of the floor of the fourth ventricle in the absence of peripheral disease (Shen 1985). In addition, bacterial overgrowth has been reported to be more common in people who drink alcohol excessively and may also contribute to upper abdominal symptoms and diarrhea (Hauge et al. 1997).

101.2.4 Alcoholic Pancreatitis

Approximately 10 % of chronic alcoholics develop attacks of clinically acute pancreatitis. Conversely, alcohol is responsible for approximately 30 % of cases of acute pancreatitis in the USA (Yang et al. 2008). In a large cohort study from the USA, alcohol was estimated to account half of the cases of chronic pancreatitis and the incidence has increased in the past 20 years (Yadav et al. 2011). Likewise, UK data reveal a correlation between rising total community alcohol consumption and the number of hospital admissions for chronic pancreatitis (Johnson and Hosking 1991).

101.2.4.1 Definitions

The term acute pancreatitis refers to an acute inflammatory process of the pancreas, with variable involvement of other regional tissues or remote organ systems. Chronic pancreatitis is characterized by chronic inflammation, glandular atrophy, and fibrosis. Clinically, it manifests pain with exocrine or endocrine insufficiency. The revised classification of acute pancreatitis identified two phases of the disease: early and late. Severity is classified as mild, moderate, or severe. Mild acute pancreatitis, the most common form, has no organ failure and local or systemic complications and usually resolves in the first week. Moderately severe acute pancreatitis is defined by the presence of transient organ failure, local complications, or exacerbation of comorbid disease. Severe acute pancreatitis is defined by persistent organ failure, that is, organ failure >48 h. Local complications are peripancreatic fluid collections, pancreatic and peripancreatic necrosis (sterile or infected), pseudocyst, and walled-off necrosis (sterile or infected) (Banks et al. 2013).

101.2.4.2 Etiology

The most common associations of acute pancreatitis in Western societies are gallstones and heavy alcohol use which together account for approximately 75 % cases. A Danish cohort study showed gallstones as the most common cause (up to 34 %) for acute pancreatitis and alcohol was the most common cause (up to 68 %) for chronic pancreatitis (Nøjgaard et al. 2010). Yadav et al. (2011) found that while alcohol was the most common etiology in men (59 %), it was a less common etiology in women (28 %). In women, both nonalcoholic and idiopathic etiologies were more common (37 % and 35 %, respectively). Nonetheless, only a minority of heavy drinkers develop clinically evident pancreatic disease.

The association between alcohol and pancreatitis appears to be dose related. Pancreatitis typically occurs in subjects who have consumed greater than 100 g alcohol per day for at least 5–10 years and rarely if ever follows an isolated alcoholic debauch.

Kristiansen et al. (2008) reviewed 17,905 Danish men and women with pancreatitis and found hazard ratios associated with drinking 1–6, 7–13, 14–20, 21–34, 35–48, and >48 drinks/week were 1.1 (95 % confidence interval (CI): 0.8, 1.6), 1.2 (95 % CI: 0.8, 1.8), 1.3 (95 % CI: 0.8, 2.1), 1.3 (95 % CI: 0.7, 2.2), 2.6 (95 % CI: 1.4, 4.8), and 3.0 (95 % CI: 1.6, 5.7). The risk of pancreatitis may be increased in developing countries as impurities within country-made alcoholic products may cause pancreatic injury (Barreto et al. 2010). In a Swedish cohort study, the risk of acute pancreatitis was associated with the amount of spirits consumed on a single occasion but not with wine or beer consumption (Sadr Azodi 2001). Acute gallstone pancreatitis occurs more often in women, while alcoholic pancreatitis occurs more often in men. Once the disease is established, episodic heavy drinking often precipitates relapses. Relapses have been described after only 1 day of recurrent drinking. Pancreatitis is common among people with HIV particularly in association with heavy alcohol use (Dutta et al. 1997; Whitfield et al. 1997). Many patients with acute alcoholic pancreatitis progress to chronic pancreatitis, with continued alcohol abuse being a key prognostic factor (Ammann 1996).

Other than gallstones, relatively common causes for pancreatitis that should be considered include hypercalcemia of any cause and severe hypertriglyceridemia. Hypertriglyceridemia (greater than 10 mmol/l (approximately 1,000 mg/dl) with lipemic serum) of any cause is associated with recurrent attacks of pancreatitis (Greenberger et al. 1966). Although alcohol abuse is a known cause of hypertriglyceridemia, the majority of cases of alcoholic pancreatitis are not associated with marked hyperlipidemia (Haber et al. 1994). Other causes include pancreatic trauma, duct pathology, and a number of drugs. In most series, about 10 % of cases are idiopathic.

101.2.4.3 Predisposing Factors

Numerous investigators have attempted to account for this individual susceptibility by studying associations between alcoholic pancreatitis and potential risk factors. These studies have been previously reviewed (Haber et al. 1995) and have focused on the amount, type, and pattern of alcohol consumption, genetic markers, diet (Wilson et al. 1985), hypertriglyceridemia (Haber et al. 1994), tobacco consumption (Haber et al. 1993), and pancreatic ischemia. The genetic markers that have been studied include blood groups, HLA phenotypes (Wilson et al. 1984), a1-antitrypsin phenotypes (Haber et al. 1991), cystic fibrosis genotypes (Norton et al. 1998), cytochrome P450 2E1 (CYP2E1) genotypes, and ADH isoenzyme genotypes. A number of these studies are difficult to interpret due to small sample sizes, inappropriate controls, and inconsistent findings between studies. There remains insufficient evidence to consider that any of the above factors are well established. A mutation of the gene coding for pancreatic secretory trypsin inhibitor (SPINK1) has been described in 5.8 % of a cohort with alcoholic pancreatitis compared with 1 % of alcoholic controls and this important observation has been independently replicated (Witt et al. 2007). Recently, mutations in chymotrypsin C (CTRC) have also been identified in pancreatitis (Rosendahl et al. 2008).

These two studies support the concept that genetic factors influence susceptibility to pancreatitis, but given that only 6 % and 3 % of the subjects carried these mutations, respectively, individual susceptibility to this disease remains largely unexplained. Two other important genetic mutations are linked to pancreatitis, but not the alcoholic form. Gain-of-function mutations in the serine protease 1 gene (PRSS1) on chromosome 7q35, which encodes cationic trypsinogen, results in an autosomal dominantly inherited form of hereditary pancreatitis. Mutations in the cystic fibrosis gene (CFTR) have been associated with an autosomal recessive form of pancreatitis.

101.2.4.4 Pathogenesis

Two important factors leading to tissue injury in pancreatitis are autodigestion and oxidant stress. Several lines of evidence indicate that activated digestive enzymes play an important role in pancreatitis (Haber et al. 1997): (a) Mutations of the cationic trypsinogen gene that increase pancreatic content of trypsin underlie hereditary pancreatitis (Whitcomb et al. 1996). (b) Activated digestive enzymes are found in both clinical and experimental pancreatitis and can produce cellular necrosis when instilled into pancreatic tissue. (c) Protease inhibitors reduce the incidence of post-ERCP and experimental pancreatitis. Oxidant stress is characterized by the production of reactive oxygen species that are atoms or molecules containing oxygen with an unpaired electron in the outer shell (free radicals). Free radicals are highly reactive and bind to lipids, proteins, and nucleic acids leading to cellular injury (Freeman and Crapo 1982). Free radicals are generated during experimental pancreatitis (Nonaka et al. 1989) from infiltrating leukocytes (Slater 1984) or possibly within acinar cells (Braganza et al. 1995).

Several mechanisms have been proposed to explain why alcohol-induced pancreatitis occurs only after many years of alcohol abuse and not after a single binge in humans. These include the role of progressive pancreatic fibrosis related to activation of pancreatic stellate cells by acetaldehyde and oxidative stress (Haber et al. 1999) and the potential for endotoxin to precipitate pancreatitis in the alcohol-exposed gland (Vonlaufen et al. 2007). Chronic alcohol intake is associated with increased gut permeability and translocation of Gram-negative bacteria across the mucosal barrier. Thus, bacterial components (endotoxins) can enter the circulation and reach the pancreas. Plasma LPS levels have been shown to be significantly higher in drinkers (either after chronic alcohol intake or a single binge) compared to nondrinkers and in patients with alcoholic liver disease compared to those with liver disease of other etiologies (Bode and Bode 2005).

101.2.4.5 Diagnosis

A confident diagnosis of pancreatitis can often be made on the basis of an attack of severe abdominal pain and tenderness with elevation of the serum amylase more than three times the upper limit of normal and with imaging studies suggestive of inflammation in and around the pancreas.

The diagnosis of alcoholic pancreatitis is occasionally difficult. The amylase level does not rise significantly in approximately 10 % of cases of acute pancreatitis, including many with alcoholic pancreatitis (Spechler et al. 1983) or in those with delayed presentation. Determination of serum lipase, which remains elevated longer than the serum amylase, may be helpful and is supplanting amylase in some centers (Gomez et al. 2012). A previous report that an increased lipase/amylase ratio was specific for alcohol-induced pancreatitis (Gumaste et al. 1991) has not been confirmed (Pezzilli et al. 1993; King et al. 1995). Newer tests that may be more specific for acute pancreatitis include trypsinogen activation peptide and trypsinogen-2 but are not widely available.

Gallstones should be excluded by ultrasound examination. In cases with a negative ultrasound, serum alkaline phosphatase or transaminase levels raised at least two-fold suggest associated gallstones which may be detected by repeat ultrasonography or endoscopic retrograde cholangiopancreatography (ERCP) (Goodman et al. 1985; Venu et al. 1983). Magnetic resonance cholangiography (Soto et al. 1996) and endoscopic ultrasound are increasingly supplanting ERCP for diagnosis of gallstones in this setting. Dilated common bile duct has been recently described in patients on methadone and with opioid dependence in the absence of gallstones (Sharma 2002).

101.2.4.6 Assessment of Severity

Several clinical findings, including thirst, poor urine output, progressive tachycardia, tachypnea, hypoxemia, agitation, confusion, a rising hematocrit level, and a lack of improvement in symptoms within the first 48 h, are warning signs of impending severe disease. If such symptoms develop, admission to an intensive care unit should be considered. Enzyme levels do not correlate well with disease severity. A number of clinical and laboratory scoring systems have been developed to identify patients at risk of complications so that they may be treated more intensively at an earlier stage.

Contrast-enhanced CT scan is now widely performed to detect pancreatic necrosis and complications of severe pancreatitis such as fluid collections, pseudocysts, and abscesses (Kivisaari et al. 1983). Some concern has been raised about possible adverse effects of contrast-enhanced CT scanning (McMenamin and Gates 1996). Studies of intravenous contrast in experimental animals have yielded conflicting findings (Foitzik et al. 1994; Kaiser et al. 1995; Schmidt et al. 1995). Caution in the unrestricted use of contrast-enhanced CT scans appears warranted. CT scanning without contrast can detect most diagnostic features of pancreatitis and is often performed. MRI is an option that may spare radiation exposure.

101.2.4.7 Treatment

Overall, about 20 % of patients with acute pancreatitis have a severe course, and 10–30 % of those with severe acute pancreatitis die. Despite improvements in intensive care treatment during the past few decades, the rate of death has not significantly declined (McKay and Imrie 2004). Severe cases, particularly those associated with respiratory or renal failure, require treatment in an intensive care unit.

Initially, patients are treated with bed rest, analgesics, intravenous fluids, and fasting. Adequate pain control requires the use of intravenous opiates, usually in the form of a patient-controlled analgesia pump. Fentanyl is being increasingly used due to its better safety profile, especially in renal impairment.

Meperidine (pethidine) has been favored over morphine for analgesia in pancreatitis because studies showed that morphine caused an increase in sphincter of Oddi pressure. However, there are no clinical studies to suggest that morphine can aggravate or cause pancreatitis or cholecystitis. It is important to note that meperidine has a short half-life and repeated doses can lead to accumulation of the metabolite normeperidine that causes neuromuscular irritation and, rarely, seizures. Morphine is more effective analgesic, is less susceptible to abuse, and is usually the drug of choice.

Ebbehøj et al. (1985) showed the use of indomethacin suppositories (50 mg twice daily) reduced opioid requirements in 30 patients with acute pancreatitis without risk of gastrointestinal bleeding. An Iranian double-blind randomized control trial showed that rectal indomethacin given immediately before ERCP reduced the incidence and severity of post-ERCP pancreatitis (Sotoudehmanesh et al. 2007).

Intravenous fluids are given aggressively to restore vascular volume and renal perfusion and hour by hour monitoring is required. Patients are initially fasted, partly for symptomatic reasons but also because early refeeding seems to cause clinical relapse. Nutritional support is required if oral intake is not likely to be restored within several days. Total parenteral nutrition (TPN) and enteral feeding (nasogastric or nasojejunal) have been evaluated. Enteral feeding is safer and less expensive and there is some evidence it may be more effective than TPN (Pandol et al. 2007). Provision of early enteral nutrition is therapeutic, changing the patient's hospital course in a favorable manner (McClave 2013).

Protease inhibitors may limit the damage done by activated digestive enzymes. In clinical practice, it is not possible to commence treatment early enough in the attack of pancreatitis for protease inhibitors to be effective, except for post-ERCP pancreatitis, where some benefit has been reported. Peritoneal lavage might improve the outcome by removing toxic inflammatory products from the peritoneum but the results of controlled studies have been conflicting (Mayer et al. 1985; Stone and Fabian 1980). Other approaches that may prove more effective include extended lavage (Ranson and Berman 1990) and retroperitoneal lavage using operatively placed cannulas (Pederzoli et al. 1990). Antibiotics have not been shown to be beneficial for unselected cases of acute pancreatitis for which the prognosis is already excellent (Bradley 1989). In severe pancreatitis, infectious complications contribute to morbidity and mortality, and several controlled trials of prophylactic antibiotic therapy have been undertaken, (Pandol et al. 2007). The results have been inconsistent and the use of antibiotics in acute pancreatitis remains controversial.

A number of antioxidant therapies have been evaluated for both acute and chronic pancreatitis given the role of oxidative stress in the pathogenesis of these diseases and encouraging results from early small trials. However, a well-conducted

recent trial in acute pancreatitis found no benefit from antioxidant supplements in predicted severe acute pancreatitis (Siriwardena et al. 2007). Similarly, the evidence is conflicted in chronic pancreatitis (see below).

ERCP with endoscopic sphincterotomy has been shown to reduce the morbidity of patients with unremitting severe gallstone pancreatitis in two randomized controlled studies (Fan et al. 1993; Neoptolemos et al. 1988). In general, ERCP should be performed within 72 h in those with a high suspicion of persistent bile duct stones (i.e., visible common bile duct stone on noninvasive imaging, persistently dilated common bile duct, jaundice, or rising liver chemistries) but plays no role in alcoholic pancreatitis.

Surgery is uncommonly required, the main indication being necrotizing pancreatitis (McFadden and Reber 1994). Observational data support delaying surgical debridement of necrotic tissue for at least two weeks if possible while the patient's medical condition is optimized and viable pancreatic tissue becomes evident. This approach appears to improve survival and maximize organ preservation. Pancreatic abscess carries a very high mortality and is an absolute indication for drainage by open surgery or percutaneous techniques. In fulminant cases, multiple procedures may be required. Small pseudocysts may resolve spontaneously but large or symptomatic ones usually require drainage via endoscopic, percutaneous, or operative techniques (Maule and Reber 1993).

101.2.4.8 Chronic Pancreatitis (CP)

Recurrent episodes of acute pancreatitis, clinical or subclinical, may lead to chronic pancreatitis. Chronic excessive consumption of alcohol is the most common cause and accounts for approximately 75 % of cases in Western societies. Interestingly idiopathic pancreatitis is the most common type in India (tropical pancreatitis) and China, accounting for approximately 70 % of all cases of CP (Garg and Tandon 2004).

101.2.4.9 Clinical Features

The main clinical problem is usually pain and this may be very challenging. Like that of acute pancreatitis, the pain of chronic pancreatitis is typically diffusely located in the upper abdomen and may radiate to the back when severe. Pain tends to increase with meals and decreases appetite and food consumption and often results in weight loss. A minority present without pain. The other manifestations are diabetes mellitus and steatorrhea. Weight loss is common but typically is mild. Vitamin deficiency is generally subclinical. Investigations may reveal malabsorption of fat-soluble vitamins and osteopenia. Other complications include pseudocyst formation, bile duct or duodenal obstruction, pancreatic ascites or pleural effusion, splenic vein thrombosis, pseudoaneurysms, and pancreatic cancer.

101.2.4.10 Treatment

Complete abstinence from alcohol is essential to minimize progression of the disease. Reassurance that the disorder is benign with a tendency to slowly remit is helpful. In patients who continue to drink alcohol, a Japanese study of 12 patients

treated with bromhexine for 6 months, eight reported symptomatic improvement, and all patients showed improvement in the levels of pancreatic enzymes (Tsujimoto et al. 2005). Non-narcotic analgesia may suffice, but opioids are often required and should not be unreasonably withheld. Olesen et al.'s (2011) Danish randomized double-blind clinical trial of 64 patients found that pregabalin compared with placebo was a more effective analgesic after 3 weeks of treatment (36 % vs. 24 %; mean difference, 12 %; 95 % confidence interval, 22–2 %; $P = .02$). Analgesic dependence or possible misuse should be carefully managed according to principles described elsewhere in this volume (Hung et al. 2001). Antidepressants should be tried. Celiac plexus injection helps about 60 % of patients but pain may recur. The procedure is not often performed due to limited efficacy, frequent recurrence, and significant complications. Pancreatic enzyme supplements have been evaluated for the treatment of pain but the evidence is mixed. A trial of 1 month is sufficient to determine whether this works in practice. Octreotide is not effective. An emerging treatment option for resistant cases of pain is total pancreatectomy with islet autotransplantation (IAT) which has shown favorable outcomes with regard to pain reduction. Concurrent IAT enabled 46 % of patients to be independent of insulin supplementation at 5 years (Bramis et al. 2012).

There is mixed evidence concerning antioxidant therapy in chronic pancreatitis. One study using a combination preparation that contained selenium, beta-carotene, vitamin C, vitamin E, and L-methionine found reduced pain and improve quality of life (Kirk et al. 2006). Antioxidants were considered useful in a subset of patients with idiopathic and obstructive but not alcoholic chronic pancreatitis in a non-randomized study (Burton et al. 2011). Recent randomized trials yielded conflicting results but antioxidant therapy was disappointing in alcoholic pancreatitis (Siriwardena et al. 2012; Braganza 2013; Bhardwaj et al. 2009).

The relationship between pancreatic duct obstruction and pain is not clear but relief of obstruction is frequently clinically associated with relief of pain. Endoscopic approaches to dilate pancreatic duct strictures and remove calculi have been developed and surgery is typically reserved for refractory cases. Extracorporeal shock wave lithotripsy (ESWL) creates millimetric fragmentation of pancreatic stones, which has improved the results of endoscopic therapy and may have additional indications in the treatment of patients with chronic pancreatitis. Whipple procedures or modified Whipple procedures are the most commonly performed procedure. The Puestow procedure (lateral pancreaticojejunostomy) involves decompression of a dilated pancreatic duct and side-to-side anastomosis onto a Roux-en-Y loop of jejunum. Two small randomized trials comparing endoscopic and surgical drainage of dilated pancreatic duct in chronic pancreatitis showed that surgery was associated with better long-term analgesia and quality of life (Cahen et al. 2007; Dite et al. 2003).

Exocrine failure is treated by dietary modification, vitamin therapy, and pancreatic enzyme replacement. Reduction of dietary fat intake reduces steatorrhea. Pancreatic enzymes are required with each meal and snack. The newer enteric-coated microsphere preparations are more potent and are preferred as they release enzymes only in the duodenum, reducing inactivation of lipase by gastric acid.

Lipase inactivation is also due to failure of pancreatic bicarbonate secretion and proton pump inhibitors may increase effectiveness of treatment. Normalization of fecal fat levels does not typically occur. Diabetes mellitus is treated with dietary modification, treatment of malabsorption, and specific therapy. Some patients respond to oral hypoglycemic agents but most require insulin. The diabetes is "brittle" in that the patient is susceptible to hypoglycemia due to loss of both insulin and glucagon secretion. Long-term surviving patients with this form of diabetes are prone to diabetic complications and should be monitored accordingly. Patients with substantial steatorrhea may require fat-soluble vitamins. The 25-hydroxylated form of vitamin D (calcifediol) is more polar than vitamin D2 or D3 and is therefore more easily absorbed in patients with fat malabsorption. The serum calcium should be monitored for the first few weeks of therapy with this naturally occurring analogue since it is more potent than vitamin D2 or D3 and can more easily produce hypercalcemia.

Small Intestine

Diarrhea is common among those who drink alcohol excessively, both acutely and chronically. Multiple factors contribute to this problem including altered motility, permeability, and nutritional disorders. Small intestinal mucosal injury can occur after acute or chronic administration of alcohol. Perfusion of the hamster jejunum with 4.8 % ethanol caused separation of the tip of the villus epithelium forming blebs (Beck 1996). These blebs may rupture leading to denudement of the epithelium. The villus core contracts and loses height within 1 min of ethanol exposure. This effect is independent of any action on the microcirculation (Dinda et al. 1994) and may be mediated by leukocytes (Dinda et al. 1996) via release of histamine from mast cells and by oxidant stress (Dinda et al. 1994).

Mucosal blood flow is acutely increased with increased endothelial permeability (Beck 1996). Acute administration of alcohol leads to increased gut permeability resulting both in abnormal absorption of luminal content (such as endotoxin, which contributes to the pathogenesis of alcoholic liver disease; see previous chapter) and abnormal leakage of mucosal contents (such as albumin). Ethanol also inhibits absorption of actively transported sugars, dipeptides, and amino acids. Many defects in absorption have been reported in people with alcohol problems, including water (Krasner et al. 1976a, b), carbohydrate, lipid, vitamins (notably thiamine, folate), and minerals (calcium, iron, zinc, and selenium) (Beck 1996). Folate deficiency, common among people with alcohol problems, causes intestinal injury leading to malabsorption and diarrhea and further loss of folate. Ethanol may exacerbate lactase deficiency, especially in non-Caucasians (Perlow et al. 1977).

Colon

Portal hypertension may manifest uncommonly with hemorrhoids and rarely with colonic varices. Colonic varices appear as filling defects on barium enema and may occur in any part of the colon, most commonly in the rectum (Feinman et al. 1992). Alcohol has also been reported to cause non-ulcerative inflammatory changes in

human colonic epithelium (Brozinsky et al. 1978). These changes resolved during a 2-week period of abstinence and were not explained by folate deficiency. This form of colitis has the potential to contribute to diarrhea but is not usually recognized clinically as pathology elsewhere in the gut tends to dominate the clinical picture.

Inappropriate alcohol enema has been reported to cause a chemical colitis (Herrerias et al. 1983) and this may result from a toxic effect similar to the direct toxicity of alcohol on the gastric mucosa. Alcohol use has a recognized association with colorectal cancer as indicated below. Finally, alcohol consumption may have at least one beneficial effect on the colon in that it has been linked to a reduced incidence of ulcerative colitis in one study (Boyko et al. 1989).

101.2.5 Alcohol and Gastrointestinal Cancer

Alcohol use is a recognized risk factor for several gastrointestinal neoplasms, including tumors of the tongue, mouth, pharynx, larynx, esophagus, stomach, pancreas, colon, and liver (Franceschi 1999; Longnecker 1995; Ringborg 1998). The effect of alcohol on cancer risk appears to be dose related. A recent comprehensive Australian overview of the literature reports that relatively modest average daily consumption, 25 g per day, within the guidelines for men in many countries including the USA, is associated with increased risk of gastrointestinal cancer. For example, consumption of 25 g per day was associated with a relative risk of 1.76 for oropharyngeal cancer and 1.52 for esophageal cancer, approximately 1.05 for colon and rectum and 1.17 for liver (Lewis et al. 2008). Cancer risk rose from zero alcohol consumption with no safe level, suggesting that the less alcohol consumed, the lower the risk of cancer.

The pathophysiology of ethanol-associated gastrointestinal malignancy is varied. Current understanding suggests that alcohol and its metabolites (in particular acetaldehyde) affect the generation of reactive oxygen species (ROS), transforming growth factor-b signaling pathways, the immune system, and cell death and apoptosis and have direct toxic effects, among them the ability to produce aberrant methylation of DNA, with an impairment of its self-repair capacity (Haas et al. 2012). Ethanol-induced induction of CYP2E1 that increases carcinogen activation, potentiation of oxidant stress, diminished DNA repair, suppression of immune responses, and nutritional depletion such as folate deficiency (Mufti 1996). For example, alcohol-fed rats given N-nitrosomethylbenzylamine developed more esophageal tumors than control rats (Mufti et al. 1989). In addition, nonalcoholic components of alcoholic beverages may in turn add to carcinogenesis. Interestingly, racial differences appear to affect the risk of carcinogenesis. In Asia, a large proportion of individuals carry a mutation of acetaldehyde dehydrogenase (ALDH) 2 which has very low activity. ALDH2 is responsible for the breakdown of acetaldehyde and thus its inhibition or reduced activity leads to an accumulation of total acetaldehyde and increased duration of exposure. Homozygotes of the

ALDH2 mutation develop severe side effects with small amounts of alcohol and hence are protected against alcohol-related disorders and alcohol overuse. In Japan, heterozygosity is prevalent in alcoholics and is significantly associated with oropharyngolaryngeal (OR 11.14), esophageal (OR 12.50), and esophageal cancer concomitant with oropharyngolaryngeal and/or stomach cancer (OR 54.20) (Yokoyama et al. 1998).

101.2.5.1 Oropharynx and Esophagus

Alcohol use is associated with an increased incidence of esophageal (and oropharyngeal) cancer, especially in those who also smoke. A Chinese population-based case–control study of esophageal cancer with 902 cases and 1,552 controls showed the combined effect of heavy smoking and drinking among men was pronounced: OR was 12.0 for those who smoked more than 1 pack per day and drank more than 750 g of ethanol per week (Gao et al. 1994). Blot et al. (1988) reported a 5.8-fold increased risk among those who drink alcohol, a 7.4-fold increased risk among smokers, and a 38-fold increased risk among those who both drank and smoked. The risk of oral, oropharyngeal, and esophageal cancer is further increased in South American countries where there is a high prevalence of concurrent alcohol, tobacco, and mate use (Wünsch-Filho 2002). A recent large meta-analysis of 20 case–control and four cohort studies including a total of 5,500 cases concluded that there was no association between alcohol drinking and esophageal adenocarcinoma risk, even at higher levels of consumption (Tramacere et al. 2012). Moderate and high alcohol intake was associated with risk of esophageal SCC. Light alcohol intake appears to be associated to ESCC mainly in studies in Asia, which suggests a possible role of genetic susceptibility factors (Islami et al. 2011). While in SCC of esophagus, the type and quantity of alcoholic beverages consumed may affect the risk of esophageal SCC. Hard liquor may have a higher risk than wine or beer; however, the cumulative amount of alcohol rather than the type is probably more important (Tuyns et al. 1979).

101.2.5.2 Stomach

The association between gastric cancer and alcohol consumption appears to be mild. Tramacere et al..'s (2012) meta-analysis of 34,557 patients provided definitive evidence of a lack of association between moderate alcohol drinking and gastric cancer risk. There was, however, a positive association with heavy alcohol drinking (RR 1.14 (95 % CI 1.08–1.21) for 50 g/day). Gastric noncardia adenocarcinomas were more common than gastric cardia cancers. This is supported by the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study which also showed beer but not wine or spirits to be positively associated with gastric cancer (Duell et al. 2012). Genetic susceptibility also appears to be important, especially in Asian populations. A Korean study showed ALDH2 polymorphisms were found to modify the susceptibility to the development of gastric cancer associated with alcohol intake, especially in case of ALDH2 *1/*2 genotype (Shin et al. 2011).

101.2.5.3 Colonic

A large pooled analysis found that those who consumed 30 to less than 45 g per day of alcohol had a relative risk (RR) of colorectal cancer of 1.16 (95 % CI 0.99–1.36) and those who consumed more than 45 g per day had an RR of 1.41 (CI 1.16–1.72); the relative risks in men and women appeared similar, and the association was seen for cancers of all portions of the colon and rectum (Cho et al. 2004). This data is reflected in the Netherlands Cohort Study which showed alcohol consumption 30 g/day or more was associated with a hazard ratio of 1.3 (hazard ratio: 1.32, 95 % CI: 1.06–1.65) [46]. Of note, cancer risk appeared to increase from proximal colon through rectum (hazard ratio: 1.29, 95 % CI: 0.85–1.96 for proximal colon cancer; hazard ratio: 1.41, 95 % CI: 0.94–2.11 for distal colon cancer; hazard ratio: 2.07, 95 % CI: 1.03–4.18 for rectosigmoid cancer; and hazard ratio: 1.69, 95 % CI: 1.08–2.64 for rectal cancer) (Bongaerts et al. 2008).

101.2.5.4 Pancreatic

The role of alcohol in pancreatic cancer pathogenesis appears to be significant. Retrospective analysis of the Swedish Inpatient Register suggested that excess risk for pancreatic cancer among alcoholics is small and could conceivably be attributed to confounding by smoking (Ye et al. 2002). High lifetime ethanol intake from spirits/liquor tends to be associated with a higher risk, but no associations were observed for wine and beer consumption (Rohrmann et al. 2009; Gapstur et al. 2011).

101.3 Prescription Medications

101.3.1 Opioids

It has long been recognized that opioids affect gastrointestinal motility. Opioids act on gut function in a complex fashion via all three receptor classes in the brain, spinal cord, and enteric nervous systems. Low doses act at enteric nervous system sites and higher doses also act within the CNS. These effects usually are manifest as constipation, but bloating, early satiety, and pain are possible. Occasionally, patients develop ileus or a syndrome characterized by a relatively high level of abdominal pain. When pain is significant, the term “narcotic bowel syndrome” has sometimes been applied (Fig. 1). It is attributed to the effects of opioid drugs on bowel function and opioid-induced hyperalgesia (Grunkemeier et al. 2007). A US survey of 98 patients with chronic non-cancer pain treated with opioids revealed constipation prevalence was 46.9 %, nausea 27 %, vomiting 9 %, and gastroesophageal reflux disease 33 %. Chronic abdominal pain was reported by 58.2 % and 6.4 % fulfilled the criteria of NBS. Prevalence of constipation increased with duration of treatment. Health-related quality of life was low in patients with chronic abdominal pain (Tuteja et al. 2010).

Opioids induce bowel dysfunction through several expected effects: blockade of propulsive peristalsis, inhibition of the secretion of intestinal fluids, and an increase in intestinal fluid absorption. Opioids decrease the activity of both excitatory and inhibitory neurons in the myenteric plexus. In addition, they increase smooth-muscle tone and inhibit the coordinated peristalsis required for propulsion, leading to disordered, nonpropulsive contractile activity, which contributes to nausea and vomiting as well as constipation. Longer gastrointestinal transit time causes excessive water and electrolyte reabsorption from feces, and decreased biliary and pancreatic secretion further dehydrates stool (De Schepper et al. 2004).

Concurrent use of other constipating drugs (e.g., tricyclic antidepressants), dehydration, advancing age, immobility, metabolic abnormalities (e.g., hypercalcemia), chemotherapy (particularly treatment with the vinca alkaloids), and tumor-related bowel obstruction may also contribute. Not all opioid formulations are equally constipating. Although the results of randomized trials are conflicting, a systematic review concluded that there is less constipation with transdermal fentanyl than with oral sustained-release morphine (Tassinari et al. 2009).

Among methadone maintenance patients, constipation is common and tends to be worse early in treatment (Langrod et al. 1981; Yaffe et al. 1973). The high prevalence of persisting constipation suggests that tolerance to the gut effects of opioids occurs to only a limited extent. In one study, 58 % of subjects in methadone maintenance experienced some degree of constipation and 10 % had severe problems (Yuan et al. 1998). Fecal impaction, and even stercoral perforation, has been described (Haley et al. 1998) and usually responds to increased fluid intake and fiber supplementation to correct for poor dietary intake. Laxatives are not often required but osmotic agents such as lactulose are the laxatives of choice.

Two peripherally acting opioid-receptor antagonists are available for the management of opioid-induced constipation: methylnaltrexone and alvimopan. They do not cross the blood–brain barrier and have no antianalgesic effect. Methylnaltrexone was approved by the US FDA in 2008 as a subcutaneous injection for the treatment of opioid-induced constipation in patients with terminal illness requiring palliative care (Thomas et al. 2008). Randomized trials report some effectiveness for oral alvimopan in the treatment of opioid-induced constipation in patients with chronic pain (Paulson et al. 2005).

101.3.2 Laxative Misuse

Surreptitious laxative misuse is among the more common causes for unexplained chronic diarrhea. It represents an intriguing form of substance misuse but is rare and is typically observed in people without other substance misuse issues. These patients present to family physicians and gastroenterologists. Some are associated with bulimia. Others tend to be older women and the disorder can be viewed as a form of Munchausen's syndrome. The diagnosis rests on identification of laxatives by stool alkalinization, osmolality studies, or a bag search in the hospital (Fine 1998).

101.3.3 Misuse of Anticholinergics

In high doses, anticholinergic drugs alter mood and are occasionally misused, particularly when prescribed to relieve extrapyramidal symptoms in the mentally ill (Caplan et al. 2007) and among those with limited access to other drugs of abuse. Amitriptyline and other tricyclic antidepressant drugs are commonly misused by people on opioid maintenance treatment (Peles et al. 2008). Clonidine and/or buscopan prescribed for opioid withdrawal may also be misused. Patients develop marked constipation and abdominal pain as well as dry mouth and blurred vision. In the author's experience, patients have had previous drug-dependence problems and have welcomed an explanation of their symptoms and participated in structured withdrawal.

101.4 Tobacco

Tobacco use is associated with a number or benign and malignant disorders of the gastrointestinal tract.

101.4.1 Gastroesophageal Reflux

Smoking has been linked to exacerbations of reflux symptoms and cessation of smoking is one of the lifestyle changes traditionally recommended in the treatment of reflux (Pandolfino and Kahrilas 2000). At a practical level, smoking cessation is difficult to achieve and has not been shown to induce remission of reflux or healing of esophagitis. Nicotine has been shown to reduce lower esophageal sphincter pressure and promote gastroesophageal reflux in response to straining during coughing and deep breathing (Kahrilas and Gupta 1990). People who smoke cigarettes have also been shown to have delayed acid clearance from the esophagus (Kahrilas and Gupta 1989). Not all studies have yielded consistent findings. One recent study found that smoking did not influence basal lower esophageal sphincter pressure or esophageal motility (Bhandarkar et al. 2000). From the foregoing, it is clear that smoking cessation cannot be recommended as sole treatment for reflux, but there is sound evidence that smoking contributes to reflux. It is reasonable to advise patients with GERD to quit smoking based upon the association with reflux, the expectation that GERD might respond favorably to quitting and to prevent the myriad of other adverse effects of smoking. Snus is a form of smokeless tobacco commonly used in Scandinavia. A Swedish study found snus significantly alters the histology of the distal esophagus but does not impact on gastrointestinal symptoms or peptic ulcer disease (Aro et al. 2010).

101.4.1.1 Peptic Ulceration

Tobacco smoking increases the risk of both gastric and duodenal ulcers as compared with non-exposed persons (Ostensen et al. 1985). Smoking increases risk of

ulcer according to the number of cigarettes smoked. Heavy smoking is associated with delayed ulcer healing and the risk of recurrence is increased (Sonnenberg et al. 1981; Korman et al. 1983). Smoking increases the risk of complications from peptic ulcer (Piper et al. 1985). Finally, the overall ulcer-related mortality is increased in those who smoke compared to those who do not (Ross et al. 1982; Kurata et al. 1986). The mechanism by which smoking exacerbates peptic ulcer disease remains unclear given several pathophysiological studies were carried out prior to the *Helicobacter pylori* era.

101.4.1.2 Pancreatic Disease

Evidence from a number of countries provides a clear link between smoking and pancreatic cancer. Several studies have consistently found a moderately increased risk (about threefold) of pancreatic cancer among smokers (Chowdhury and Rayford 2000; Talamini et al. 1999).

There have been inconsistent findings concerning the relationship between smoking and pancreatitis (Chowdhury and Rayford 2000). A case–control study compared tobacco use in a group with alcoholic pancreatitis and a control group who drank at least as much alcohol yet did not develop pancreatitis and found no association with smoking (Haber et al. 1993). A French study of 108 patients concluded that tobacco intake accelerates the course of alcoholic chronic pancreatitis in a dose-dependent fashion with a threshold at 20 pack-years (Rebours et al. 2012). Overall, it would seem appropriate to recommend patients with alcoholic pancreatitis quit smoking, in addition to other risks of smoking.

101.4.2 Inflammatory Bowel Disease

A curious relationship exists between smoking and inflammatory bowel disease. A meta-analysis of 22 studies showed an association between current smoking and Crohn's disease (OR, 1.76; 95 % confidence interval [CI], 1.40–2.22) and former smoking and ulcerative colitis (OR, 1.79; 95 % CI, 1.37–2.34). Current smoking had a protective effect on the development of UC when compared with controls (OR, 0.58; 95 % CI, 0.45–0.75) (Mahid et al. 2006). Smoking status is also strongly associated with microscopic collagenous and lymphocytic colitis. The risk is higher in current smokers and is not significantly affected by gender or alcohol consumption (Yen et al. 2012).

Smokers are more than twice as likely to develop Crohn's disease as nonsmokers (Silverstein et al. 1989). Smoking may also increase the risk of recurrence of Crohn's disease. At least one study suggested that patients who stop smoking for more than 1 year can decrease the risk of flares (Cosnes et al. 2001). Tobacco smoke appears to interfere with epithelial integrity and immune responses to pathogenic bacteria but research in this area is ongoing (Verschuere et al. 2012).

Patients with ulcerative colitis who begin smoking after the diagnosis of their disease present a significant reduction in the number of recurrences (Fraga et al. 1997), and hospitalization and surgical procedure occur most frequently in heavy smokers who quit smoking before the onset of ulcerative colitis (Boyko et al. 1988). This suggests nicotine may have a therapeutic potential for this disease. Nicotine influences immune cellular function, increases mucin production, relaxes colonic smooth muscle, increases endogenous glucocorticoids, and influences rectal blood flow and intestinal permeability (Thomas et al. 2005). Less toxic approaches to this form of therapy have been sought and include topical colonic administration of nicotine. These approaches remain experimental at this time (Lunney and Leong 2012). McGrath et al.'s Cochrane Review (2004) of transdermal nicotine patches for the treatment of mild to moderate ulcerative colitis has suggested that these agents can improve ulcerative colitis compared to placebo but have significant adverse events and have not been shown to be more effective than other effective treatments.

101.4.3 Gastrointestinal Malignancy

Smoking has been strongly linked to cancers of the upper gastrointestinal tract and pancreas as discussed above. The link between smoking and stomach cancer is weaker but is present in most studies (Neugut et al. 1996; Trédaniel et al. 1997). A Swedish population-based prospective cohort of 17,118 twins with up to 30 years of follow-up showed long-term heavy smoking was associated with a statistically significant threefold increased risk of colorectal cancer compared with never smoking (relative risk 3.1, 95 % CI 1.4–7.1). Examining colorectal cancer sub-sites separately, a nonsignificant 60 % increased risk of colon cancer was observed only for heavy smokers and a statistically significant fivefold increased risk was observed for rectal cancer (Terry et al. 2001).

The risk is related to total number of cigarettes smoked and the duration of smoking. Pipe and cigar smoking have a higher risk compared with cigarette smokers (Franceschi et al. 1990). Interestingly, a recent meta-analysis of smokeless tobacco (snus or snuff) available in Scandinavia has shown to be not associated with cancers of the oropharynx, esophagus, stomach, and pancreas once the effects of smoking are removed (Lee 2011).

Tobacco smoke contains multiple mutagenic and carcinogenic compounds including nicotine, nitrosamines, and polycyclic hydrocarbons. Mouse and cell models reveal a direct promoting action of nicotine on the growth of gastric tumor and neovascularization through sequential activation of the ERK/COX-2/VEGF signaling pathway (Shin et al. 2004). The effects of tobacco and alcohol appear to be synergistic. Smoking increases the acetaldehyde burden following alcohol, and alcohol enhances the activation of various procarcinogens via cytochrome P450 induction.

101.5 "Body Packing"

Persons smuggling illicit drugs may ingest large amounts of cocaine, heroin, or other drugs aiming to retrieve the packages after reaching their destination (Traub and Kohn et al. 2003a). This is referred to body packing, cocaine packing, or body stuffing syndrome (Malbrain et al. 1994). Multiple packages made from latex condoms, wax, or plastic bags are either swallowed or placed retrogradely into rectum or vagina. The incidence of this practice is unknown. Most cases present in police custody raising ethical and potentially funding challenges of managing an involuntary patient. Some people may be coerced to smuggle drugs. Cases involving children and pregnant women have been described (Traub et al. 2003a, b). Hospitals close to international airports may encounter these cases and should consider developing a management policy for this challenging problem. An early report describes 10 cases diagnosed only after death in which as many 147 packages were found (Wetli and Mittlemann 1981). Lethal drug absorption through rubber condoms may occur without rupture. The body packer may present with life-threatening symptoms of intoxication, including seizures and cardiorespiratory collapse, as well as mechanical obstruction from the ingested drug packets. The distal ileum was the most common site of obstruction, whereas rupture tended to occur in the upper gastrointestinal tract (East 2005). The largest series comprises 61 cases from Milan, Italy, of which only two cases required laparotomy, one each for obstruction and nonfatal drug toxicity (Aldrighetti et al. 1996).

Plain X-ray is the method of choice to detect drug-filled packets within the gastrointestinal tract of body packers (Hergan et al. 2004). Dilute contrast has been reported to assist identification of the packages (Gherardi et al. 1990). In some cases, CT is required, with potential concerns regarding radiation exposure if repeated examinations are needed. Extensive dose reduction makes low-dose CT a valuable alternative imaging modality for the examination of suspected body packers and might replace conventional abdominal radiographs as the first-line imaging modality (Maurer et al. 2011).

Clinical monitoring comprises frequent clinical and neurological assessment and abdominal examination daily to the detected complications of acute drug intoxication or bowel obstruction or perforation. The patient should be kept in hospital until all drug packages have cleared due to the risk of life-threatening overdose if any rupture. Traub et al. (2003) presented a detailed review and clinical approach to management. A light solid diet with free liquids may be given. Oily or polyethylene glycol laxatives can be given repeatedly to accelerate passage of packages (Hoffman et al. 1990). Symptomatic cases may require early surgery (Silverberg et al. 2006). The risk of careful endoscopic removal from the esophagus is probably exaggerated, and in any case, the risk of endoscopic removal is almost certainly less than that of any other surgical approach to the esophagus. The rigid esophagoscope appears to have an advantage over the flexible instrument because of the wide lumen which will accommodate most average-sized pellets. Intact pellets in stomach and small bowel may be retrieved endoscopically or are evacuated through a single gastrotomy and/or enterotomy. Non-obstructing pellets in the colon pose an

interesting dilemma. Removal through a colotomy will expose the patient to the risk of sepsis. The risk of rupture of pellets already in the colon must be very low as there are no noxious enzymes here and the pellets are subject to less turbulence within formed stool than they would be in the small intestine (East 2005).

Methamphetamine body stuffers have similar demographics to those of body stuffers of other stimulants but tended to ingest fewer baggies with larger masses and had a higher percentage of severe outcomes (29 %) than previously reported with other stimulants. Increases in presenting pulse rate and temperature (pulse rate 120 beats/min or 38.0 °C) are common in patients who will develop end-organ damage (West et al. 2010).

101.6 Psychostimulants

Gastrointestinal disorders are uncommon in patients with stimulant use. Juxtapyloric perforation has been described after the smoking of crack cocaine in 50 (95 % male) consecutive patients (Feliciano et al. 1999). Cocaine abuse can cause mesenteric ischemia and gangrene, which result in small and large bowel perforation as well as intraperitoneal hemorrhage (Tiwari et al. 2006). This is thought to be related to cocaine-induced arterial vasospasm or vasoconstriction leading to intestinal ischemia with mucosal and transmural necrosis as well as mesenteric vascular thrombosis. The use of preoperative angiography is vital in detecting occlusive lesions that are amenable to revascularization (Hoang et al. 1998). The usual management of small or large bowel gangrene or perforation is by resection and primary anastomosis.

101.7 Cannabis

Our understanding of cannabis and cannabinoid substances has changed since the discovery of the endocannabinoid system (ECS). Cannabinoid receptors are widely expressed throughout both the upper and lower GI tract and are also expressed on hepatic stellate cells. Consequently, cannabinoids may influence a range of GI functions in health and disease (Pertwee 2001). Cannabinoids have been implicated in the pathophysiology of satiety, nausea/emesis, gastrointestinal secretion, gastrointestinal motility, gastrointestinal sensation, as well as inflammation (Izzo and Sharkey 2010). Nausea and vomiting are side effects of many chemotherapeutics and reduce the quality of life of patients with diabetes, cancer, and acquired immune deficiency syndrome. Cannabis (marijuana) and other cannabinoids appear to be effective antiemetics. The antiemetic effect has been demonstrated in an animal model and is related to the expression of CB1 receptors in the dorsal vagal nucleus (Van Sickle et al. 2001). Cannabinoids are also involved in inhibition of gastric emptying and gastric acid secretion.

Cannabis has also been linked to a series of cases with hyperemesis (Allen et al. 2004). Cessation of cannabis, as confirmed by a negative urine drug screen for

cannabinoids, led to cessation of the cyclical vomiting illness and a return to regular cannabis use heralded a return of the hyperemesis weeks to months later. The hyperemesis is often relieved by frequent hot showers (Sontineni et al. 2009). The mechanism is not understood. A further similar case was described in the UK (Roche and Foster 2005) and a small series has now been reported in the USA (Soriano-Co et al. 2010). Most recently, a series of 98 cases was reported from the Mayo Clinic (Simonetto et al. 2012). Cannabinoid hyperemesis should be considered in younger patients with long-term cannabis use and recurrent nausea, vomiting, and abdominal pain.

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Liver Disorders (Incl. Hepatitis) in IVDAs

102

Giorgio Barbarini and Alessandro Perretti

Contents

Abstract

In the human body, the liver is the most susceptible organ to injury by foreign molecules, as a consequence of its primary role in their metabolism and of its position as the first organ encountered by ingested substances after absorption. When any drug or toxin is abused heavily, the liver can be overwhelmed with the task of processing it out of the body, resulting in liver damage and liver failure. Because in any urban area worldwide (but in many countries also in

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nonurban areas) a constant progression of drug addiction is reported, liver diseases induced by this behavior represent a growing challenge for all clinicians confronting a patient with liver injury. Drug-induced liver injury can present in a clinical pattern similar to acute hepatitis, chronic hepatitis, acute liver failure, biliary obstruction, or fatty liver disease; furthermore, the link of drug addiction with HBV and HCV infection, very common among drug abusers either IV or not IV, can make liver diseases worse; so today, drug addicts have to be considered at very high risk of liver damage. The literature on drug-induced liver injury is large, sometimes controversial, but dispersed to publications in many disciplines, often appearing as short reports or letters; in the classical textbooks on drug-induced liver diseases, most of the considered drugs, except alcohol, are commonly medically prescribed drugs, even if several hundreds of them have been linked to liver damage.

102.1 Introduction

In the human body, the liver is the most susceptible organ to injury by foreign molecules, as a consequence of its primary role in their metabolism and of its position as the first organ encountered by ingested substances after absorption. When any drug or toxin is abused heavily, the liver can be overwhelmed with the task of processing it out of the body, resulting in liver damage and liver failure. Because in any urban area worldwide (but in many countries also in nonurban areas) a constant progression of drug addiction is reported, liver diseases induced by this behavior represent a growing challenge for all clinicians confronting a patient with liver injury. Drug-induced liver injury can present in a clinical pattern similar to acute hepatitis, chronic hepatitis, acute liver failure, biliary obstruction, or fatty liver disease; furthermore, the link of drug addiction with HBV and HCV infection, very common among drug abusers either IV or not IV, can make liver diseases worse; so today, drug addicts have to be considered at very high risk of liver damage. The literature on drug-induced liver injury is large, sometimes controversial, but dispersed to publications in many disciplines, often appearing as short reports or letters; in the classical textbooks on drug-induced liver diseases, most of the considered drugs, except alcohol, are commonly medically prescribed drugs, even if several hundreds of them have been linked to liver damage. In the first part of this chapter, we try to summarize the most relevant informations available today about liver injury due to the use/abuse of cocaine, ecstasy, heroin, marijuana, methamphetamine, steroids, inhalants, and alcohol; in the second part, we analyze the impact of HBV, HCV, and HDV infection on the liver of drug addicts.

102.2 Liver Toxicity of Considered Drugs

102.2.1 Cocaine

Cocaine is one of the most addictive and dangerous drugs of abuse; its medical complications can include cardiovascular, cerebrovascular, renal, muscular, and

liver injuries. Cocaine-induced hepatotoxicity may be sometimes fatal, usually hours to a few days after an overdose, generally following or accompanying other major organ involvement (myocardial infarction, stroke, rhabdomyolysis, and renal failure are the most frequent); the cause of death is generally not due only to an acute liver failure but to a multi-organ failure. Clinically, the pattern of cocaine-related hepatic injury is usually an acute necrosis (centrilobular and periportal necrosis with diffuse micro- and macrovesicular fatty infiltration have been histologically demonstrated) with very high levels of serum aminotransferases and a rapid decrease of prothrombin value (possible DIC). Cocaine is believed to cause liver damage by conversion to a toxic metabolite as a result of P450 metabolism. Liver damage is more common, and the risk of a sudden death is estimated 18 times greater, when cocaine and alcohol are used together than when cocaine is used on its own. In the most part of cases, the liver injury due to cocaine is self-limited and resolves rapidly; there is no specific therapy or antidote for acute cocaine hepatotoxicity. Because the liver damage cocaine-related is similar to the one due to acetaminophen, infusions of N-acetylcysteine are often given in these situations. Also crack can produce a very similar hepatotoxicity, and some years ago also cases of fulminant hepatitis B were observed after crack use. Chronic hepatic damage linked only to cocaine use, without alcohol and without HBV and HCV infection, has not been sufficiently demonstrated.

102.2.2 Ecstasy (MDMA)

Many cases of acute liver failure after ecstasy use have been reported in recent past years, with a Zenit in the second half on the 1990s. The clinical features may differ from acute liver failure with hyperthermia to acute liver failure without hyperthermia or to mild hepatitis. The mechanism of MDMA-induced hepatic damage is unclear because histological changes varying from a mild to moderate lobular hepatitis to massive hepatic parenchymal collapse with areas of nodular regeneration and cholestasis have been described; the severity of liver failure does not seem to correlate with the amount or the frequency of ingested MDMA, suggesting an individual susceptibility for the related hepatic damage (single cases of recurrent hepatitis after ecstasy exposure have been reported). Ecstasy users may be also at increased risk of heatstroke because of the direct effect of MDMA on thermoregulation via central serotonergic nerve terminals, in addition to high exercise levels, inadequate fluid replacement, and the high temperatures often present at "raves." In acute liver failure with hyperthermia, it is difficult to establish if ecstasy is directly hepatotoxic or if liver injury results from the hyperthermia; the clinical resulting failures generally need liver transplantation. In acute liver failure without hyperthermia in the most part of described cases, liver damage can progress often to severe and liver transplantation is needed. In mild liver failure without hyperthermia, the patients can recover themselves without developing severe coagulopathy or encephalopathy. MDMA is generally not detectable in the urine or blood of patients admitted to the hospital for liver failure after ecstasy use,

because of the short half-life of the drug and the usual ingestion and presentation. In young patients admitted to the hospital, presenting an unexplained acute hepatic damage, it is important to verify the possible drug history, both oral and intravenous. The mechanism by which MDMA causes liver disease is unknown, but all amphetamines undergo extensive hepatic metabolism particularly by hepatic P450 system (CYP 2D6) with generation of a liver toxic metabolite.

102.2.3 Heroin

The liver damage due to pure heroin is relatively small, not significant; this drug is metabolized very quickly and does not affect liver functions in a big way. Heroin itself is also nontoxic to the liver like to any other internal organs; however, additives and dilutants with which street heroin is generally "cut" can cause after prolonged use of IV heroin some damage to the liver. The most important effect of heroin on the liver is due to HBV and HCV infections, very common among IVDA; drug users' liver failure is often linked to their physical health because it is notorious that the most part of them are malnourished and generally unhealthy. Only in very few papers, a direct hepatotoxicity of heroin, consisting in vesicular hepatotoxic changes and fatty changes not linked to alcohol or hepatitis viruses, has been demonstrated, but not confirmed in subsequent research.

102.2.4 Marijuana

The prevalence of cannabis use among young people everywhere in the world is no less than 10–20 %; just a few days ago, data from the Italian Public Health Ministry revealed a percentage of 25 % of regular cannabis users among young students aging from 14 to 18. Medical consequences of regular cannabis usage are still debated; today, cannabis is known to have some therapeutic potential in treating multiple sclerosis, asthma and breathing difficulties, migraine headaches, and severe pains. Cannabis is used in some countries, including the USA and Canada, as antiarthritic, antidepressant, and/or anticonvulsant. In a controversial study published (2008) in Clinical Gastroenterology and Hepatology, Norah Terrault and colleagues demonstrated a significant association between daily versus non-daily cannabis use and moderate to severe fibrosis, especially in HCV-positive patients and in HIV/HCV-coinfected people; the Liver Transplant Center of Michigan University (David Nicholas Ranney and coll.) concluded, upon a multivariate analysis, that survival in transplanted subjects is associated not only with MELD score and HCV infection but also with marijuana use, considered a significant negative factor. Other studies however showed beneficial effects of cannabis use in people treated for HCV with antiviral specific therapy (PEGIFN plus Ribavirine) helping the patients to maintain the adherence to the therapy. Just less than one year ago, a poster by Italian researchers at EASL annual conference postulated that a cannabinoid receptor (CB2-63 QQ Variants) is associated with a more severe liver damage in HCV-positive people.

102.2.5 Amphetamines

In several clinical trials, amphetamines (not MDMA, previously described) have not been associated with serum aminotransferase elevations; nevertheless, some cases of hepatic injury have been reported in international literature but usually only after amphetamine, often used intravenously, overdoses. The liver injury due to amphetamines is generally self-limited and resolves rapidly.

102.2.6 Anabolic Steroids

Synthetic androgenic steroids, medically used for male sex hormone replacement, are widely assumed for body building because of their anabolic effects; many of them can cause cholestatic liver injury, and after a long-term use, they can be associated with liver tumors. The C-17 alkylated androgenic steroids have been implicated either in the acute or in the chronic liver injuries, while the esterified testosterones have not been implicated in the acute, but only in a lower rate of chronic liver diseases. The mechanism of hepatic injury is not well defined for the acute cholestatic disease, while an unregulated growth stimulus to hepatocytes is the cause of nodular regeneration and hepatic tumors. The onset of acute liver damage after anabolic steroids is often insidious, with nausea, fatigue, and itching, followed by dark urine and jaundice. Jaundice and pruritus can be prolonged also after a promptly steroid discontinuation; AST, ALT, and ALP levels may be often normal also with a high bilirubinemia. Liver histology shows a typical bland cholestasis with minimal inflammation and hepatocellular necrosis; bile duct injury is generally mild and vanishing bile duct syndrome rare. Chronic injuries related to anabolic steroid abuse are peliosis hepatis, nodular regeneration, hepatic adenomas, and hepatocellular carcinoma. Peliosis hepatis is a rare syndrome, with normal or mildly elevated serum enzyme levels, in which there are blood-filled enlarged sinusoids and cysts throughout the liver. Patients may complain of right upper quadrant discomfort with hepatomegaly or abdominal pain and vascular collapse due to hepatic rupture and hemoperitoneum. Peliosis hepatis associated with anabolic steroid abuse generally reverses, at least in part, stopping drug assumption. Nodular regeneration has been described as a marked nodular regenerative hyperplasia with portal hypertension and splenomegaly, often found in "normal livers"; generally, the course of this illness is asymptomatic or associated with mild abdominal discomfort linked to hepatomegaly. Hepatic tumors are typically found in subjects on long-term anabolic steroids (5–15 years, but onset within 2 years of drug use has been described); histologically, they may look as hepatic adenomas, as "well-differentiated" hepatocellular carcinomas or as hepatic adenomas with areas of malignant transformation. Clinical presentation usually shows right upper quadrant discomfort and a hepatic mass on imaging procedures; routine liver tests are often normal before an extensive spread of the tumors. It is often possible to obtain a spontaneous regression of adenomas after stopping anabolic steroid use.

102.2.7 Inhalants

Chronic inhalant abuse can cause significant damage to the liver, depending on the time duration of the drug abuse. The hepatic injury seems to resemble alcoholic disease; carbon tetrachloride has such a strong association with liver damage that is today used to induce liver injury in some animal models.

102.2.8 Alcohol

The association of alcohol abuse and liver damage is well known and documented from the times of ancient Greeks and Ayurveda's system of medicine. Because there is evidence suggesting that fermented beverages existed at least as early as the Neolithic period (app. 10,000 BC), alcoholic liver disease (ALD) should be considered the oldest form of liver injury known to mankind. In the 1830s, the link between alcohol consumption and fatty liver was described in European medical literature, but the pathogenesis of this disease has been associated almost exclusively with a secondary protein and choline deficiency. Only in the last 1940s the direct toxicity of ethanol, its metabolism, and its metabolites have been demonstrated to represent the pathogenetic stimulus for alcoholic liver damage; nevertheless, today also we have to admit that our knowledge of ALD pathogenesis is not complete. In fact, the susceptibility to develop ALD is strictly individual and the reason unknown; the basic mechanism behind alcohol-induced cell death has not been unfolded, although the direct hepatotoxicity of ethanol has been established in experimental animals. Alcohol is the most common cause of liver diseases in the Western countries, but everywhere in the world, the percentage of alcoholic hepatic damages is still growing. In 2004, 3.8 % of all global deaths were attributable to alcohol, 6.2 % for men and 1.1 % for women, in 30 % of them due to liver failure. The harmful use of alcohol is the leading risk factor for death in men aged 15–59; the highest proportion of alcohol-attributable mortality is in the Russian Federation and neighboring countries, where 5 % of deaths among men and 6 % among women are attributable to the harmful use of alcohol. Relatively high numbers of alcohol-attributable deaths were revealed also in economically expanding middle-income countries, such as Brazil and China. Worldwide, alcohol consumption in 2005 was equal to 6.13 l of pure alcohol consumed per person aged 15 years or older. Analysis from 2001 to 2005 showed that countries in the WHO Americas, European, Eastern Mediterranean, and Western Pacific regions had relatively stable consumption levels during that time, while marked increases were seen in Africa and Southeast Asia. The main causative factors in alcoholic liver disease are as follows:

102.2.8.1 Quantity and Duration of Alcohol Use

Among susceptible people, risk increases markedly for men drinking >40 g (particularly >80) of alcohol/daily for >10 years; if consumption exceeds 230 g/daily, the risk of cirrhosis is about 50 %. The type of consumed alcohol may influence the risk to develop ALD; in a survey of more than 30,000 subjects in

Denmark, drinking beer or spirits was more likely to be associated to ALD than drinking wine. Nevertheless, only some chronic alcohol abusers develop liver disease; also variations in alcohol intake do not fully explain variations in susceptibility, suggesting that other factors are involved.

102.2.8.2 Sex

Women are more susceptible to alcoholic liver injury, even after adjustment for body size; they require half quantity of alcohol (20–40 g/daily) than for men to be at risk which may be increased if their alcohol dehydrogenase (ADH) level in the gastric mucosa is less.

102.2.8.3 Genetic Factors

Alcoholic liver disease often runs in families worldwide. Asians, who have lower levels of acetaldehyde dehydrogenase (ALDH), are more susceptible to toxic acetaldehyde effects. In the USA, the rates of alcoholic cirrhosis are higher in African/American and Hispanic males than in Caucasian, and the mortality rates are the highest in Hispanics.

102.2.8.4 Nutritional Status

Undernutrition (specially for protein), diets high in unsaturated fat, and obesity increase the susceptibility to ALD.

102.2.8.5 Other Factors

HBV, HCV, and HDV hepatitis and iron accumulation in the liver are concomitant high risk factors for the development of ALD.

Fatty liver, **alcoholic hepatitis**, **cirrhosis, and hepatocellular carcinoma** are the spectrum of alcohol-related hepatic injury, often as separate, progressive manifestations, but sometimes not necessarily distinct stages of evolution, simultaneously present in a given individual. The pathophysiology of ALD is linked to the metabolism of alcohol; ethanol is readily absorbed from the stomach and the small intestine and catabolized in the liver (only a small amount is degraded in transit through the gastric mucosa) involving ADH, cytochrome P450, and microsomal enzyme oxidation system (MEOS). ADH, a cytoplasmic enzyme, oxides alcohol into acetaldehyde subsequently oxidized to acetate by ALDH, a mitochondrial enzyme. These oxidative reactions generate hydrogen, which converts nicotinamide-adenine dinucleotide (NAD) to its reduced form (NADH), increasing the redox potential (NAD/NADH) with an inhibition of fatty acid oxidation and gluconeogenesis and promoting fat accumulation in the liver. Hepatic fat accumulation may predispose to oxidative damage subsequently increased by endotoxins, released in the gut, which stimulate liver macrophages (Kupffer cells) to release free radicals. Oxidative damage is increased also by liver hypermetabolism, due to alcohol consumption; by reduction in protective antioxidants (e.g., glutathione, A and E vitamins); by binding of alcohol oxidation products, such as acetaldehyde, to liver cell proteins, forming neoantigens and resulting in inflammation; by accumulation of WBCs attracted by lipid peroxidative damage and neoantigens; and finally by inflammatory

cytokines secreted by WBCs. As a result, cell necrosis and apoptosis with hepatocyte loss and subsequent fibrosis, stellate cells, lining sinusoids (blood channels) in the liver, proliferate and transform in myofibroblasts, with an excess of collagen and extracellular matrix that narrow the sinusoids limiting blood flow. Fibrosis narrows the terminal hepatic venules, contributing to portal hypertension; extensive fibrosis is associated with an attempt at regeneration, resulting in liver nodules that represent the first step of cirrhosis. Clinically, ALD shows an initial fatty liver (steatosis), with a macrovesicular fat hoard, potentially reversible, followed by alcoholic hepatitis (steatohepatitis), a combination of fatty liver, diffuse liver inflammation, and liver necrosis (balloon degeneration and Mallory bodies) with subsequent extensive fibrosis that disrupts the normal liver architecture evolving in cirrhosis. Symptoms are usually absent in patients with fatty liver, may appear (fatigue, fever, jaundice, tender hepatomegaly) during alcoholic hepatitis and compensated cirrhosis, ranging from mild to severe, and are evident in decompensated cirrhosis (ascites, portal-systemic encephalopathy, variceal bleeding, liver failure with hypoglycemia, coagulopathy, and hepatorenal syndrome). Hepatocellular carcinoma develops in 10–15 % of patients with alcoholic cirrhosis; the percentage is more elevated if other factors (hepatitis virus infection, hemochromatosis) are concomitant.

102.2.9 Hepatitis Viruses and Drug Use

Injection drug users (IDUs) are, from many years, the subjects at highest risk for acquiring hepatitis B, C, and D virus infection not only in developed but also in developing countries; in fact, there is a high efficiency transmission of these viruses via blood exposure. Declines in use of drug preparation and injection equipment have been observed in the HIV era (1990s) and have been associated with reduction over time in HCV-HBV-HDV infection among IDUs. However, injection-risk behavior has not totally been eliminated and sharing of drug preparation equipment, such as drug cookers and filtration cotton, seems to persist in IDUs. Furthermore, among heroin and cocaine noninjection drug users (NIDUs), there are other risk factors such as transmission through the sharing of equipment which could convey the viruses to denuded nasal mucosa or practices such as tattooing and perhaps also piercing; finally, sexual intercourse is generally inside the drug users group, a very closed group. High HCV incidence and rapidly increasing HCV prevalence were and are observed among young IDUs, and factors associated with HCV contagion include recent initiation to injecting, unstable housing, female gender, ethnicity, survival sex work, imprisonment, frequent injecting heroin or cocaine use, and having a partner who injects. The high risk of HCV infection among younger and recent IDUs indicates a narrow window of opportunity for prevention, with estimates of the median time to HCV infection of about 3 years.

102.2.9.1 Epidemiology

In 2007, it was estimated that there were 15.9 million IDUs worldwide and that inside them no less than ten million have been exposed to HCV with eight million

of chronic infection. The largest populations of HCV-positive IDUs lived in Eastern Europe (2.3 million) and eastern and southeastern Asia (2.6 million): The three countries with the largest populations of HCV-positive IDUs were China (1.6 million), Russia (1.3 million), and the USA (1.5 million). Some epidemiological studies revealed that in 2010, about 1.2 million of IDUs were HBsAg positive, with an IDUs global prevalence of 8.45 %. The largest populations by region are Asia and Southeast Asia.

The local epidemiology of HCV, HBV, and HDV infection among IDUs has been evaluated in several clinical studies. In 1991, Thomas and colleagues found a prevalence of HCV antibodies in 89 % of IDUs in Baltimore, Maryland, USA. Fortunately, a decline of this prevalence was observed by *Des Jarlais and colleagues* among IDUs in New York from 1990 to 2001: 90 % to 63 % during that period. A study conducted by Centers for Disease Control and Prevention showed that injection drug use was the first risk factor for HCV infection in the USA from 1984 to 2001. *Stroffolini et al*. determined in 2009 the prevalence and characteristics of HCV infection in a national sample of drug addicts in Italy. 543 drug addicts were enrolled: anti-HCV prevalence was 63.9 %; HCVRNA was detected in 68.3 % of patients positive for anti-HCV. They found a major prevalence of genotypes 1 (especially 1a) and 3 (49.3 % and 39.7 %, respectively). Prevalence of HBsAg was 2.8 %, while HDV markers were not determined. Probably, a growing concern of the risk of acquiring infectious diseases from blood, in particular HIV infection, contributed to the decline in HCV incidence.

Hepatitis B outbreaks among IDUs are occurring with an increasing incidence, and this in spite of the availability of effective vaccines for more than 20 years, especially in countries where vaccination is not mandatory. HBV infection among IDUs, in fact, depends on the population surveyed. In 1996, a study of *Garfein et al*. revealed that the seroprevalence of HBV positivity among a population of 716 IDUs with up to 6 years of drug use was 65.7 %. However, a recent study of *Baklan et al*. in 2004 showed that the prevalence of HBV infection in a group of IDUs in maintenance methadone program was only 17 % and only one among them exhibited signs of active infection. In any case, all studies demonstrated that methadone program is protective in terms of HBV infection.

HDV is a defective RNA-containing passenger virus requiring helper functions provided by HBV including provision of the hepatitis B surface antigen coat for virion assembly and penetration into hepatocytes. Transmission of HDV occurs through the same modalities of HBV transmission, and the most important factor influencing efficiency of transmission is whether the exposed individuals are or are not carriers of HBV. In a study of *Chen et al*., over 628 IDUs' antibodies against HDV were found in 68.1 % of individuals testing positive for HBsAg. However, in a study of *Huo et al*., over 494 IDUs in 2004 showed that 87 patients (18 %) were HBsAg carriers and only 12 (14 %) were anti-HDV positive; the prevalence rate of HDV was significantly lower than that in 1985. In a recently published work (2011), Paul Nelson and colleagues reviewed more than 5,000 abstracts, papers, and online resources reporting an estimate of global prevalence and population size for HCV and HBV infections in IDUs living in 77 countries in the world.

102.2.9.2 Management and Treatment of HCV Infection

The pharmacotherapeutic treatment of HCV in the general population has made great progress in recent years. The use of peginterferon and ribavirin plus boceprevir or telaprevir, new protease inhibitors against HCV, has significantly increased the rate of SVR (sustained virological response) in patients with genotype 1 without decompensated cirrhosis. Genotypes 1a and 3, as above reported, are more prevalent in IDUs and they affect treatment duration and response. A liver biopsy, when feasible, is indicated in order to identify the level of fibrosis and the causes of liver damage (viral, toxic, steatosis, or others). A very important problem in IDUs is represented by potential drug interactions between peginterferon and methadone or alcohol use. Interferon seems to increase serum levels of methadone especially in the presence of alcohol. Furthermore, alcohol dependence in IDUs decreases treatment response rates to interferon therapy. Interferon-based regimens for hepatitis care are often complicated by neuropsychiatric adverse effects (depression in particular). Patients should be screened for depression and other mental health problems before beginning treatment with interferon, treated if necessary and monitored for these problems during treatment for HCV. Nevertheless, past episodes of depression or other psychiatric disorders are not an absolute contraindication to treatment for HCV. For many years, in the past, illicit drug use has been considered a contraindication to antiviral therapy for chronic hepatitis C. Actually, several studies show that adherence and therapeutical success in IDUs are similar to other patients. A study of *Zanini et al*. in 2010 analyzed 16 prospective studies and data from a cohort of 953 IDUs treated for HCV infection. The estimated overall SVR and dropout rates were 52 % and 26 %, respectively. The rate of psychiatric severe adverse events that led to treatment discontinuation was 2 %. These prevalences were not significantly different from those reported in registration trials of treatment of the normal population. Since the population of IDUs is not a homogeneous group, it was very important that the different subgroups could be studied: active IDUs, IDUs in methadone maintenance program, IDUs in alternative detoxification program, and former IDUs since multiple years. *Guidelines for the management of chronic hepatitis C in patients infected after substance use* in 2005 established that active IDUs will not be eligible for antiviral treatment, but decisions about antiviral treatment should be made by a multidisciplinary treatment team together with the patient based on individualized risk-benefit assessments. *Bruggmann et al*. demonstrated that active intravenous drug use during chronic hepatitis C therapy does not reduce sustained virological response rates in adherent patients. *Belfiori et al*. in 2008 evaluated efficacy, safety, and tolerability of a standard peginterferon alfa-2a or alfa-2b plus ribavirin treatment in IDUs who were receiving methadone or buprenorphine. The results indicate that patients on maintenance treatment can be treated for HCV with a good success rate and tolerability. In conclusion, adherence is the most important factor for the success of therapy. The multidisciplinary team (infectivologist, psychiatrist, and others) is the key to obtain good adherence and compliance. This is a fundamental theme. In June 2009, in Bologna, FederSerD (Federation of Italian SerDs, public structures for the care of drug addiction) organized a conference on

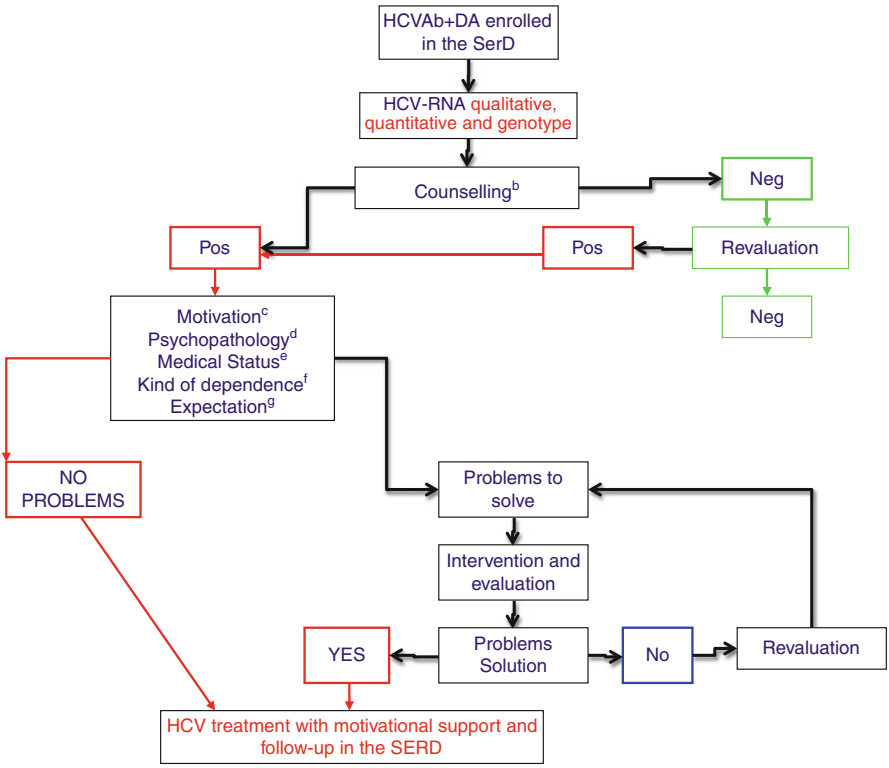

Fig. 102.1 Level of readiness for HCV treatment in IDUs

infectious diseases in IDUs. A working group (experts in addiction medicine, hepatologists, psychiatrists, psychologists, and nurses) presented a multidisciplinary model of care of HCV infection in IDUs. Because the major barriers to adherence to this therapy have been considered a lack of information about self-management, difficulty with motivation, and a lack of support for behavioral changes, we considered necessary that patients have to be informed, motivated, and skilled in the use of cognitive and behavioral self-regulation strategies to cope effectively with treatment-related demands. This model of intervention includes screening and treatment for HCV infection among IDUs; counselling pretreatment, during treatment, and posttreatment; psychiatric evaluation and enhanced cooperation with hepatologists/infectivologists, and following the steps represented in Fig. 102.1. Just after the Bologna Conference, an observational, multicenter study based on this model started under the surveillance of FederSerD; all enrolled patients are followed in the SerDs by addiction specialists together with infectivologists/hepatologists, psychiatrists, nurses, social workers, and counselors. About 40 % of patients are followed with a DOT (directly observed therapy), and the preliminary results have been presented at the 2011 and 2012 AASLD. We think

that our preliminary results emphasize either the epidemiological importance, for public health safeguard, to treat HCV-related CAH in IDU, or the feasibility and effectiveness of anti-HCV treatment in these subjects, if it may be adequately managed by a multidisciplinary team. SerDs represent the place where experts in addiction medicine, infectivologists, hepatologists, psychiatrists, psychologists, nurses, and social workers can work together caring for the "patient with his ill" in an atmosphere in which therapeutic means are explored, the regimen is explained, adherence is discussed, follow-up is planned, and DOT is often possible. So the adherence and the compliance to treatment regimens may be also better than in the general population because IDUs are monitored and supported during the treatment in the structure where they feel "a friendly care."

102.2.9.3 Management and Treatment of HBV/HDV Infection

Treatment indications of active HBV infection in IDUs are nearly the same of the common people. A liver biopsy, when feasible, is indicated in order to identify the level of fibrosis and to quantify cytoplasm and nuclear HBV markers. HBVDNA quantitative determination is very important to know the viral activity and decide the beginning of antiviral therapy. Peginterferon alfa-2a has been registered for the treatment of chronic hepatitis B at the dosage of 180 mcg for 48 weeks in both HBeAg-positive and HBeAg-negative patients. In IDUs, this therapy presents all the problems above reported and linked with peginterferon use. Entecavir and tenofovir, nucleos(t)ide analogs, inhibit HBV replication by competing with the natural nucleoside triphosphates for incorporation into viral DNA. They are generally well tolerated with few side effects. A monitoring of renal function during tenofovir use is requested. Interactions between tenofovir and entecavir with methadone or buprenorphine have not been pointed out.

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Renal/Metabolic Consequences of Drug/Alcohol Use

103

Annemarie Hennessy

Contents

Abstract

This chapter outlines the indirect and direct effects of illicit *drug use* and alcohol on the kidneys and the renal tract. The classification of renal involvement as acute kidney injury or chronic kidney disease and the potential sites in the kidney for renal damage are outlined. These effects range from prerenal and hemodynamic effects which are rapidly reversible with appropriate treatment to intractable intrinsic renal disease directly related to drug or alcohol ingestion. The potential mechanisms of renal dysfunction are discussed. It also examines some of the chronic disease consequences of drug use such as blood-borne

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infection which have complex renal involvement. Rhabdomyolysis is also explored here. Considerations of renal replacement therapy in the setting of drug use and end-stage renal disease are discussed. The metabolic effects of marijuana, alcohol, amphetamines, and MDMA are outlined.

103.1 Introduction

Renal disease is broadly defined by the effect it has on either immediate- or long-term renal function: acute kidney injury versus chronic kidney disease. Acute kidney injury (AKI) is defined as an acute decrease in urine flow and/or an acute rise in serum creatinine (a manifestation of a rapid decline in glomerular filtration rate). Chronic kidney disease is defined as a long-term alteration in renal function including abnormal urinary sediment, which may or may not be associated with a slow and progressive decline in glomerular filtration rate. It is these patients who are destined for renal replacement therapy, either dialysis or eventually, transplantation. It is common for indirect renal injury to arise from the hemodynamic and other systemic complications of drug taking including alcohol overdose.

Alternatively, direct renal injury and thus renal disease are defined by the part of the nephron that is most likely affected: glomerulus, tubules, renal interstitium, or blood vessels. It is more likely that tubular and vascular injury will result from drugs of addiction. It is much less common for glomerular injury to occur in this setting. The clinical terminology for glomerular disease is based on old-fashioned syndromal definitions, i.e., nephrotic and nephritic syndrome, or asymptomatic urinary abnormality such as proteinuria or hematuria. Any of these can be caused *directly* from drugs of addiction or alcohol but are more likely when they occur to be part of a complex chain of end-organ damage arising indirectly from the consequences of drug taking.

This chapter will review these indirect injury and direct injury pathways in the kidneys from alcohol and other drugs of addiction (Table 103.1).

103.2 Renal/Metabolic Consequences

103.2.1 Alcohol

103.2.1.1 Acute Alcohol-Related Injury

Cases of acute tubular injury have been associated with acute alcohol binging, but these reports are usually confounded by nonsteroidal anti-inflammatory use or rhabdomyolysis (Johnson and Wen 1995). The combination of an analgesic agent often used for alcohol-related symptoms such as headache (e.g., NSAID) which also diminishes glomerular filtration rate, in addition to the compromise of renal perfusion pressure (dehydration) seen as a result of alcohol-related inhibition of AVP (Coiro et al. 2009), is causative in this setting (Cecchin and De Marchi 1996).

103.2.1.2 Chronic Alcohol-Related Injury

Alcohol has profound renal effects as early as at the time of in utero renal development (3–6 weeks of embryonic life). There are now animal models which indicate a direct renal effect with decreased nephron number after in utero exposure to low-dose ethanol (Probyn et al. 2012). Renal injury has been associated with fetal alcohol syndrome (Qazi et al. 1979).

Alcohol is associated with a number of adult renal conditions. IgA disease (deposition of IgA in the mesangium of the glomerulus) can arise from hypergammaglobulinemia in the setting of alcoholic cirrhosis (Tissandie et al. 2011). The recent discovery of identifiable glycosylation properties of IgA in the setting of alcoholic cirrhosis indicates "unique biological properties" of circulating immune complexes which differentiate this type of secondary from primary IgA disease (Novak and Julian 2011). Rates as high as 64 % of autopsies from chronic alcoholics show evidence of renal IgA deposition (Smith and Hoy 1989).

Direct "alcohol nephrotoxicity" described in the 1960s was invariably associated with progressive and cirrhotic liver disease (Laube et al. 1967). It was more likely a manifestation of the association of advanced liver disease with renal failure (hepatorenal syndrome). It is now known that this injury is not specific to alcohol-related hepatic injury.

Hepatorenal syndrome is a well-described and often terminal complication of cirrhosis of all causes. This is diagnosed where there is a slow decline in renal function at the time of decline in hepatic function. Often the rise in serum bilirubin is a close marker of deterioration. It is almost invariable association with portal hypertension. The theories of cause link increased intra-abdominal pressure with the hypoperfusion of the kidneys, in a setting where blood volume is also reduced due to hypoalbuminemia. There is a concurrent increase in plasma renin activity. Hepatorenal syndrome is classified as type 1, an acute deterioration in GFR with a prognosis of 2 weeks, and type 2, slower onset and associated with ascites, with a prognosis of 6 months. Treatment of type 1 disease is with appropriate supportive care: hemodynamic restoration including active upper GIT bleeding, treatment of bacterial peritonitis, and albumin replacement; the addition of terlipressin, a vasopressin analogue, significantly improves survival and transplant-free time, with a relatively low complication rate and an 8 % recurrence rate for the hepatorenal syndrome (Sagi et al. 2010).

Alcohol has been associated with renal urothelial cancer (Probert et al. 1998), although this tracked with beer above other types of alcohol intake. The decreased risk of prostate cancer as conferred by folate intake (Roswall et al. 2013) is not altered by alcohol intake.

Alcohol has an indirect effect on renal function in the longer term by means of chronic hypertension (Klatsky et al. 1977) initially thought to be independent of age, sex, weight, smoking habit, and social class. Due to the contribution of alcohol to caloric intake, it also contributes to obesity and thus risk of diabetes mellitus. The relationship between alcohol and diabetes mellitus is complex as moderate consumption is associated with reduced incidence of diabetes (Mukamal et al. 2003). Less commonly chronic pancreatitis from alcohol intake can lead to diabetes

Table 103.1 Drug-specific effects on the kidney and renal tract

Pattern of injury	Substance use association
Indirect renal injury associated with drug use	
Prerenal failure/acute tubular necrosis in the setting of cardiogenic shock, hypovolemia, multiorgan failure, or septic shock	Any overdose leading to cardiogenic shock or hypovolemia
	Significant drug overdose including acute alcohol poisoning
	Hepatorenal syndrome associated with advanced cirrhosis from alcohol
	Significant (overwhelming) bacterial infection
Rhabdomyolysis	Significant drug use or overdose including acute alcohol poisoning, cocaine, MDMA and narcotic use, and overdose (prolonged immobilization)
Renal involvement in systemic infection including bacterial endocarditis and other intravascular infections	Intravenous drug use – any agent
Blood-borne virus infections with renal consequences	
Hepatitis C-related cryoglobulinemia	
Hepatitis B-related minimal change or	
Membranous nephropathy or	
Mesangiocapillary glomerulonephritis	
HIV-related nephropathy	
Hypertension and extrarenal vascular damage including accelerated atherosclerosis	Cocaine, methamphetamines, and heroin
Malignant hypertension	Chronic alcohol, MDMA
	Cocaine
Renal epithelial cell cancers (bladder and ureters)	Chronic alcohol
Obstructive uropathy	Rare cases with MDMA
Direct renal parenchymal injury from drug use	
Glomerular injury	Chronic alcohol
Secondary IgA disease from alcoholic liver disease	
Nephrotic syndrome/nephritic syndrome	
Acute glomerulonephritis (including post-infectious glomerulonephritis)	Cocaine and heroin – IV contamination with staph or strep and nasal disruption
Anti-glomerular basement disease (rare)	Cocaine
Amyloidosis	Skin-injected heroin
Tubular injury	
Acute tubular nephrotoxicity	Cocaine and heroin
Acute interstitial nephritis	Rare cases with MDMA
Vascular injury	Cocaine and amphetamines/MDMA
Renal arterial vasospasm, segmental infarction, drug-induced vasculitis	

mellitus (present in 50 % of chronic pancreatitis) and thus is a risk factor for diabetic nephropathy (Lowenfels et al. 1993); pancreatitis is not seen in acute alcohol binges (DiMagno and DiMagno 2012; see ▶ Chap. 101, "Gastrointestinal Disorders Related to Alcohol and Other Drug Use"). Healthy heart guidelines targeting weight and blood pressure will include a component recommending safe alcohol consumption parameters for men and women in order to decrease risk of pancreatitis-induced diabetes and alcohol-related hypertension (Bulpitt 2005) among other recognized alcohol-related complications.

103.2.2 Cocaine and Renal Injury

The commonest direct renal injury arising from cocaine use is renal infarction arising from intense renal arterial vasospasm and renal artery (or segmental artery) thrombosis (Zimmerman 2012). This is thought to be contributed to by the combination of vasoconstrictive sympathomimetic and prothrombotic mechanisms. The possible use of combinations of vasoactive and renal hemodynamic acting drugs (including NSAIDs) cannot be underestimated in this setting.

Other direct renal toxicity has recently been described in the form of antiglomerular basement membrane disease (Goodpasture's disease). This has been associated with intranasal and smoked "crack" cocaine use (Peces et al. 1999) and other modalities (Chan et al. 2011). Antiglomerular basement membrane disease presents as a rapidly rising creatinine, acute pulmonary hemorrhage, and pulmonary edema with an active urinary sediment (red cell casts). Rapid treatment with hemodialysis and immunosuppression or plasmapheresis is usually indicated for the specific treatment of uremia and for decreasing the circulating antibody. Other supportive measures including blood transfusion for pulmonary hemorrhage and treatment of hypertensive emergencies may be required.

As well as the indirect effect of hypertension on long-term renal function, cocaine contributes to glomerular damage and fibrosis due to effect on the RAAS (renin-angiotensin-aldosterone system) and endothelin-1. Nonspecific lesion has been identified in the glomerulus, tubules, and interstitium of animals and in human chronic exposure. These abnormalities contribute to progression to ESRD (end-stage renal disease) requiring chronic dialysis in some cases.

Indirect renal injury is most commonly due to rhabdomyolysis (Jaffe and Kimmel 2006). Other indirect effects are due to hypertension including malignant hypertension and accelerated atherosclerosis (Lange and Hillis 2001). Proteinuria is inevitably described in those scenarios and the patients are not often biopsied leaving open the possibility that there is coexistent glomerular injury (Jaffe and Kimmel 2006).

103.2.3 Amphetamines and Derivatives and Renal Effects

MDMA and other amphetamine derivatives are most commonly associated with AKI. When used in the setting of dance parties and other events associated with

extreme exertion and even seizures, the principal effect is a prerenal insult related to severe dehydration. AKI is further compounded by the presence of acute muscle injury and toxicity from muscle breakdown products in the form of rhabdomyolysis where pigmented toxins cause a direct tubular injury.

On rarer occasions and often with single-dose use, vascular injury in the form of acute segmental infarction has been described (Woodrow et al. 1995; Citron et al. 1970). Also, acute proximal tubular injury has been described (Kwon et al. 2003). It has also been noted that bladder outlet obstruction can be caused by some other unexpected cholinergic effect of these poorly controlled drugs (Bryden et al. 1995). Individual variation attributable to routine dose toxicity is thought to be related to cytochrome and metabolism genetic variations (de le Torre et al. 2004).

These insults are largely thought to be reversible when the acute intoxication has been treated with intravenous fluids and careful management of body temperature, dehydration with fluids, and urinary pH in the setting of rhabdomyolysis.

103.2.4 Heroin and Renal Injury

Historically, heroin-associated nephropathy was thought to be due to contaminants (bacterial or viral) or poor quality heroin or morphine as the incidence of these has declined in the era of proven blood-borne virus-related nephropathy. The data from the 1970 to 1980s suggested a range of nephrotic syndrome relating to minimal change lesions, mesangiocapillary lesions, but, more commonly, focal sclerosing glomerulosclerosis. This was most common in African-Americans of that era. This lead to end-stage renal failure, and the degree of tubule-interstitial scarring at the time of the initial diagnosis, as with most glomerular disease, is indicative of the prognosis.

Immune complex-mediated glomerular disease (presenting as nephrotic or nephritic syndrome) has been associated with chronic staphylococcal and streptococcal infections in the setting of either intravenous use or due to nasal disruption from intranasal administration (Koyama et al. 1995).

There are case reports of renal amyloidosis arising from chronic skin infection after subcutaneous use (Jacob et al. 1978).

Infective endocarditis is the most common direct intravascular infection still common in IV drug users. The renal complication of this is a manifestation of infectious vasculitis with mycotic involvement (bacterial microabscesses) as well as necrotizing segmental infarction from septic emboli. There are also immune complex-mediated inflammatory changes in the glomeruli including crescent formation and rapidly progressive renal injury. The presentation is most usually nephritic syndrome (hypertension and hematuria) but in 14 % of cases can be nephrotic with normal blood pressure. The severe forms of renal failure require support with dialysis, but the mainstay of treatment is the treatment of the underlying bacterial infection. In the case of large-sized valvular vegetations or mycotic aneurysm, cardiothoracic surgery or intravascular surgery may be required.

103.2.5 Intravenous Drug Use and Indirect Renal Effects

The commonest renal consequence of any IVDU is related to infections, either post-streptococcal acute glomerulonephritis or due to the renal effects of bacterial endocarditis or other intra-arterial vascular infection as outlined above. The mechanisms of renal injury here include acute glomerular injury, post-streptococcal glomerulonephritis and nephritic syndrome, and immune complex deposition disease from endocarditis. In the longer term, GN related to blood-borne virus (BBV) infection causes a significant burden of disease.

103.2.6 BBV in Drug Users and Renal Consequences

The viral consequences of IVDU and blood contamination include infection with hepatitis B and C and HIV.

Hepatitis B is associated with membranous nephropathy and mesangiocapillary pattern (membranoproliferative) glomerulonephritis, the former presenting as nephrotic syndrome (more commonly in infected children) and the latter as nephritic syndrome with progressive renal failure if left untreated. Males are more likely to be affected. This was described with case reports dating back to 1984 (Akinsola et al. 1984). The other rarer manifestations are minimal change nephropathy (nephrotic syndrome) and polyarteritis nodosa (an aggressive form of glomerular disease associated with progressive renal damage). These are widely thought to represent a spectrum of immune disease ranging from in situ immune reactions to hepatitis antigens present in various components of the glomerulus (membrane and subepithelial locations) to the deposition of immune complexes arising from the chronic antigenemia in the circulation (Venkataseshan et al. 1990; Adeyi 2009). Treatment strategies in hepatitis B-related GN have targeted reduction of proteinuria and maintenance or improvement of renal function (serum creatinine) with only marginally beneficial results from a combination of immunosuppressive therapy and antiviral treatment (Zheng et al. 2012). There are considerable implications for the management of hepatitis B in the setting of renal transplantation should that be required (Kalia et al. 2011) (Table 103.2).

Hepatitis C can be associated with cryoglobulinemic renal disease which can rapidly progress to AKI and irreversible renal injury. Specifics of treatment relate to viral control predominantly, but the need for aggressive renal management including plasma pheresis can be indicated in severe cases.

HIV-associated nephropathy has the following pathological presentations: immunotactoid deposition glomerular disease and HIV (viral) nephropathy. These are rare (Chen et al. 2011). There is considerable overlap in the literature with coinfection with hepatitis B and C and HIV, and therefore, the causal relationships with individual infections are still not entirely clear.

Other psychotropic drugs have not been associated with glomerular or other renal diseases. Kava has been associated with increased rates of nephropathy

Table 103.2 IVDU viral infections and their associated glomerular complications

Hepatitis B	Membranous glomerulonephritis
	Membranoproliferative glomerulonephritis (MPGN)
	Polyarteritis nodosa (PAN)
Hepatitis C	MCD ?coincidental
	Membranoproliferative glomerulonephritis (MPGN)
HIV	Immunotactoid GN (rare)
	HIV nephropathy (rare)

(proteinuria) and transitional epithelial cell hyperplasia and cancer potential renal tract cancers in animal studies (National Toxicology Program 2012).

103.2.7 Rhabdomyolysis and Its Management

Rhabdomyolysis is the commonest form of indirect renal injury, and this can arise from significant drug use or overdose including acute alcohol poisoning, cocaine, MDMA and narcotic use, and overdose (prolonged immobilization). It is of particular concern in the setting of dehydration, hyperthermia, and drug toxicity from MDMA used in dance settings. The specific pathophysiological abnormalities include direct tubular toxicity from myoglobin metabolites such as ferrihemate, vasoconstriction from these agents, and lipid peroxidation. There are myoglobin casts in tubules which cause obstruction.

The diagnosis of rhabdomyolysis is confirmed by the concentration of creatine kinase (CK) in the circulation. For acute kidney injury, generally high CK levels ($>$15,000 U/l) are required except when the rhabdomyolysis is accompanied by acidosis, dehydration, and/or sepsis. Cytokine release has also been described.

Treatment is mainly focused on fluid resuscitation and restoration of electrolyte disturbances. This is best performed with extremely close attention to the repeated measurement of urine electrolytes including urinary pH, normalizing serum potassium, sodium, and chloride and by establishing a reasonable urine output (0.5 ml/kg/h), although much high targets ($>$2.5 ml/kg/h) are desirable. There is limited level A evidence for urinary alkalinization (urine Ph $>$ 7.0) (Tolouian et al. 2005) which is often very difficult to achieve in clinical practice. In severe cases, dialysis may be required for 3–6 weeks.

103.2.8 Renal Replacement Therapy: Dialysis and Renal Transplantation in the Setting of Drug Use and End-Stage Renal Disease

Although end-stage renal disease rarely arises de novo from drug use, this has been described with prolonged MDMA and cocaine use and malignant hypertension.

Providing long-term dialysis to individuals with drug and addiction issues can be complex. Issues of vascular access, repeated intravascular infection, difficulties with pain management, and compliance with fluid restriction regimes are just a few of the complications.

Transplant in addicted individual poses particular challenges. These largely relate to the acute surgical issues, such as pain management, and longer-term issues, such as immunosuppression, and infection and cancer risk. Poor compliance issues are largely thought to be the main contributor to poor renal graft survival in ages 15–25 years (ANZ data); addictive drug behavior and poor adherence lead to the same poor outcomes from the point of view of the kidney function after transplantation but also for the patient overall (reduced patient survival). There is no evidence that substance abuse relapses after transplantation, but the presence of intercurrent either alcohol-related injury (especially hypertension and cardiomyopathy) or hepatitis C infection in IV drug users poses increased risks after transplantation.

103.2.9 Metabolic Consequences of Marijuana

There are no direct renal consequences of marijuana use, but recently a case report of metabolic disturbances in the setting of diabetes has arisen (Hennessy et al. 2011). It is postulated that the acid-base disturbance arising in diabetic ketoacidosis has a different acid-base profile and attention to ketosis is an essential component to safe management in this setting. The confounding comorbidity here is vomiting. There is another anecdotal evidence of hyperemesis with heavy cannabis use which will independently lead to mild hypokalemia and a low serum bicarbonate (Wild and Wilson 2012). The association of intractable vomiting with excessive hot water bathing has been noted (Nicolson et al. 2012). In general, the longer-term metabolic derangements from marijuana relate to liver and lipid dysfunction (Muniyappa et al. 2013).

103.2.10 Metabolic Consequences of Alcohol

The commonest metabolic abnormalities arise from chronic alcohol use and are indirect in that they are secondary to excessive vomiting/gastritis, chronic diarrhea, and pancreatitis.

Electrolyte disturbance from alcohol-induced diarrhea is well reported (Testino 2008). There are additional complications related to specific inhibition of magnesium absorption and phosphate malabsorption, but the major pathology is from rapid GIT transit time, mucosal damage, and a range of gastropathies (gastritis, ulceration, and paresis).

Acute and chronic effects of alcohol on arginine vasopressin (AVP) function are also important in electrolyte balance. Acute alcohol ingestion leads to

a demonstrable increase in urine flow as a direct result of inhibition of AVP. Alcohol further disrupts the AVP response to rising electrolyte concentrations and perpetrates the hemoconcentration (Rubini et al. 1955). This effect is seen in both acute and chronic ingestion but seems in part to be moderated by age. Despite this direct water balance effect mediated by hormones, the net effect of very large intakes of hypotonic fluids is a hyponatremic syndrome. This is usually a conflation of low-salt food intake at the same time. Alcohol also has a direct effect in acute doses on sodium, potassium, and chloride excretion. Hypophosphatemia is generally thought to be related to poor nutrition in a chronic setting. Direct muscle toxicity from alcohol can lead to a mild hyperphosphatemia. Chronic alcoholic intake has in the past been shown to be the commonest cause of hypomagnesemia (Epstein 1992). The mechanism of this deficiency is most likely due to increases in urine flow rate but can also effect tubular magnesium exchange (Romani 2008). Calcium excretion is similarly increased with alcohol use.

The hemodynamic response to alcohol has in part been shown to be related to changes in renin secretion (Puddey et al. 1985). This may account for some of the additional changes seen with alcohol use including hypokalemia and a systemic alkalosis.

103.2.11 Metabolic Consequences of Cocaine and Narcotic Use

As MDMA use, cocaine has been associated with malignant hyperthermia, excessive sweating, and fluid losses and with the development of rhabdomyolysis. These are the same mechanisms which contribute to the development of hyponatremia in some cases. Hypoglycemia has also been described.

103.2.12 Metabolic Consequences of Amphetamines and MDMA

The use of MDMA causes a direct increase in body temperature and ability to exercise excessively. This response has been associated with rhabdomyolysis as described above but has also been associated with hyponatremia related to excessive drinking with its use.

MDMA has a complex interaction with water balance leading to well-documented cases of water intoxication and hyponatremia; these cases have been described after a single use but will also occur with accumulated doses. The profound hyponatremia was largely thought to be due to water intoxication in the setting of dehydration and excessive sweat loses, but a high rate of this abnormality with MDMA would suggest that an additional effect is in play – the AVP effect of MDMA on decreasing water losses and decreasing aquaporin.

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Neurobiological Complications of Substance Abuse

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Abstract

Drugs of abuse can impinge upon an individual's brain function and produce myriad neurobiological consequences. Drugs of abuse can produce neurobiological complications during acute intoxication, after withdrawal, and/or as a consequence of long-term abuse/dependency. Whether a direct or indirect consequence, substance abuse can induce severe negative neurobiological complications acutely or chronically. Cellular pathologies may include microglial activation, neuronal cell loss, gliosis, and axonal damage.

104.1 Introduction

In 2012, an estimated 23.9 million Americans were current (past month) illicit drug users. This estimate represents 9.2 % of the population aged 12 years or older, an increase of over 8 % in just 10 years' time (NSDUH 2013). Drugs of abuse can impinge upon an individual's brain structure and function to produce myriad neurobiological consequences. Substances of abuse can induce severe negative neurobiological effects directly or indirectly, acutely or chronically. For example, consequences such as seizures or stroke can occur almost immediately upon intoxication, whereas encephalopathy is more likely to develop chronically. Continued abuse, in many instances, can lead to substance-use disorders that are frequently associated with comorbid functional deficits in working memory, attention, and decision-making. A diminution in executive functioning can result in aggressive, sexual, and/or other behavioral activities that lead to further destructive personal and social health.

In addition to medical complications, persons with substance-use disorders are at risk for potentially severe social and occupational adverse consequences. Individuals with substance-use disorders are more likely to be unemployed and less likely to find a job compared to people who are not dependent. Substance abuse increases the risk of domestic violence in families. Children of substance-abusing parents are at higher risk for poor social, educational, and health functioning and are more prone to abuse drugs themselves.

Neurobiological complications can be associated with intoxication, dependence, and/or withdrawal depending upon the type of drug abused. Drugs can initiate a cascade of intertwined direct (e.g., toxic) and indirect (e.g., vascular) within the central nervous system (CNS). Nearly all drugs of abuse affect adversely the frontal/prefrontal circuitry of the brain, areas that are important for controlling decision-making and mitigating impulsivity. In terms of direct actions, several aspects of drug intoxication may lead to cellular pathology and likely underlie medical consequences. These can be increased neuronal cell loss, neurodegenerative-related modifications, a reduction of astrocytes, widespread axonal damage, and/or microglial activation (Buttner 2011).

As a substance-use disorder develops, there is an increasing difficulty for an individual to prevent the compulsive abuse of drugs. The overlap of brain areas

involved in substance-use disorders indicates that brain changes stemming from abuse may interact to precipitate the other. For example, associated changes in schizophrenia may increase the vulnerability to substance abuse or vice versa. This added layer of complexity involving comorbid disorders may increase the likelihood for, or enhance the severity of, the neurobiological complications of substance abuse.

104.1.1 Substance Abuse as a Part of Substance-Use Disorders

Substance-use disorders develop along a clinical continuum. An individual develops a substance-use disorder at different rates depending on one's genetic makeup, environment, the substance or substances being abused, and the route by which a substance is introduced into the body (e.g., oral, inhalation, injection). The faster a substance with an addictive liability enters the body and reaches its active site(s) in the brain, the more likely that substance will be abused.

Intoxication is associated with recent substance abuse. It can involve either a drug or a chemical toxin and has the potential to develop into maladaptive substance-use disorder with repeated use or abuse.

Repeated abuse of drugs frequently results in homeostatic adaptations that buffer or diminish the effects of a drug. This is drug tolerance. Tolerance varies based upon the type and quantity of the drug taken and is associated need for markedly increased amounts of the substance to achieve the previously experienced level of intoxication.

Withdrawal is the group of symptoms that occurs upon the abrupt discontinuation or markedly reduced intake of a chronically abused substance. Withdrawal only develops after an individual has developed a physical dependence to a given substance. Withdrawal symptoms generally present as opposite of the drug's direct effects on the body. For example, withdrawal from a sedative such as alcohol or barbiturates can result in rebound hyperexcitability and an increased likelihood for the onset of generalized tonic-clonic seizures.

Substance abuse was previously considered to pertain to those individuals who did not yet meet the criteria for dependence; however, the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), no longer separates abuse from dependence. Instead, the DSM-5 now combines abuse and dependence categories into a common "substance-use disorder." These are frequently associated with "substance-induced disorders," such as intoxication and withdrawal, depending on the drug of abuse (see Table 104.1) (American Psychiatric Publishing Group 2013).

Because neurobiological complications of substance abuse can occur during any of the aforementioned "phases" of substance abuse – acute intoxication, as a consequence of long-term abuse/dependency, or withdrawal – associated consequences of various classes of drugs of abuse are presented along this "continuum" below.

Table 104.1 DSM-5 diagnoses as they relate to various classes of drugs. The neurobiological complications associated with these various drug classes vary based upon the associated severity of drug abuse as presented within the context of these clinical diagnoses

Drug class	Drug examples	Clinical diagnoses
Cannabis	Marijuana	Cannabis intoxication
		Cannabis use disorder
		Cannabis withdrawal
Hallucinogens	Lysergic acid diethylamide	Phencyclidine intoxication
	Phencyclidine (angel dust)	Phencyclidine use disorder
	Psilocybin (mushrooms)	Other hallucinogen intoxication
	Mescaline (peyote)	Other hallucinogen use disorder
		Hallucinogen persisting perception disorder
Inhalants	Toluene	Inhalant intoxication
	Butane	Inhalant use disorder
Opioids	Hydrocodone	Opioid intoxication
	Hydromorphone	Opioid use disorder
	Oxycodone (oxycontin)	Opioid withdrawal
	Heroin (opiate)	
	Morphine (opiate)	
Stimulants	Cocaine	Stimulant intoxication
	Amphetamine	Stimulant-use disorder
	Methamphetamine	Stimulant withdrawal
	3,4-Methylenedioxy-N-methamphetamine (MDMA, ecstasy)	
Sedatives	Alcohol (ethanol)	Alcohol intoxication
	Benzodiazepines	Alcohol-use disorder
	Barbiturates	Alcohol withdrawal
		Sedative, hypnotic, or anxiolytic intoxication
		Sedative-, hypnotic-, or anxiolytic-use disorder
		Sedative, hypnotic, or anxiolytic withdrawal
Tobacco (nicotine)	Cigarettes	Tobacco-use disorder
	Smokeless tobacco	Tobacco withdrawal

104.2 Neurobiological Consequences

104.2.1 Neurobiological Complications of Substance Abuse

Neurobiological complications arising from six major classes of drugs of abuse are discussed including:

1. Cannabis (e.g., marijuana, synthetic cannabinoids)
2. Hallucinogens (e.g., LSD, PCP)

3. Inhalants (e.g., toluene, butane)
4. Opioids (e.g., oxycodone, heroin)
5. Stimulants (e.g., cocaine, amphetamines, bath salts, ecstasy, nicotine)
6. Sedatives (e.g., alcohol, benzodiazepines)

104.2.2 Cannabis

Cannabis (marijuana) is one of the most commonly used/abused drugs worldwide, behind caffeine, alcohol, and tobacco. In the United States, marijuana was the most commonly used illicit drug in 2012 with 18.9 million past-month users (NSDUH 2013). Marijuana use and abuse has increased dramatically among young people since 2007; there are now more adolescent marijuana smokers than there are cigarette smokers.

Marijuana consists of the dried flowers of cannabis plants which are selectively bred to produce high levels of THC and other psychoactive cannabinoids such as cannabidiol. The principal psychoactive ingredient responsible for the euphoria associated with marijuana abuse is delta-9-tetrahydrocannabinol (THC). Marijuana is typically smoked or consumed orally.

"Spice" refers to a wide variety of herbal mixtures containing synthetic cannabinoids that produce psychoactive experiences similar to marijuana. Spice products are sold under many names such as K2, fake weed, Yucatan Fire, Skunk, or even Moon Rocks. These products are marketed as "safe," legal alternatives to marijuana (National Institute on Drug Abuse 2012c).

104.2.2.1 Neurobiological Mechanisms of Action

THC is a partial agonist for CB1 and CB2 cannabinoid receptors. CB1 receptors are dispersed widely throughout the CNS including the basal ganglia, substantia nigra, hippocampus, and cerebellum. When activated, CB1 receptors inhibit presynaptically both glutaminergic and GABAergic interneuronal neurotransmission, whereas CB2 receptors are expressed mainly in the immune cells of the periphery. Because THC activates CB1 receptors in the CNS, it is considered to be responsible for mediating the addictive effects of marijuana.

104.2.2.2 Acute Intoxication

Marijuana abuse can result in increased appetite, heightened sensory perception, inattentiveness, cognitive dysfunction, motor incoordination, an altered perception of time, and talkativeness. It can also impair short-term memory. Effects can vary dramatically for individuals and, when smoked, typically persist for 1–3 h (National Institute on Drug Abuse 2012a).

With heavier marijuana smoking, toxic psychosis, hallucinations, paranoia, and a loss of the sense of personal identity can occur. Neurovascular complications have also been reported with heavy abuse, although these data are preliminary. As with other substances of abuse, the proposed mechanisms for marijuana-induced ischemic events include vasospasm, vasculitis, and/or orthostatic hypotension (Tamrazi

and Almast 2012). Because confiscated samples of marijuana have demonstrated that THC content has increased significantly over the past three decades, complications of heavy marijuana abuse may become increasingly more common (National Institute on Drug Abuse 2012a).

A variety of neurobiological complications have also been described for spice or K2 abusers who have been taken to Poison Control Centers. Some complications that have been reported include the following: elevated heart rate, nausea, agitation, confusion, and hallucinations. Spice can also raise blood pressure, can produce myocardial ischemia, and, in rare instances, has been linked to heart attacks (National Institute on Drug Abuse 2012c).

104.2.2.3 Complications of Dependence

Chronic marijuana smoking can result in dependence. Although the DSM-5 does not define a "cannabis-use disorder," neurobiological complications stemming from chronic marijuana abuse may increase anxiety and depression and/or contribute to an amotivational syndrome. Although research has not yet determined whether marijuana is causally linked, or is only correlated with, these mental health issues, there is some evidence to suggest that there may be a link between chronic marijuana abuse and schizophrenia (National Institute on Drug Abuse 2012a).

104.2.2.4 Withdrawal

Regular smokers of marijuana or abusers synthetic cannabinoids can experience withdrawal and addiction symptoms. With repeated abuse, CB1 receptors can homeostatically downregulate, which may contribute to cannabis-induced withdrawal symptoms when drug use is abruptly discontinued. Some of the neurobiological complications that regular marijuana smokers may experience during withdrawal may consist of restlessness, anorexia, irritability, and, perhaps most prominently, insomnia.

104.2.3 Hallucinogens

Hallucinogenic compounds are found in mushrooms and some plants. Common hallucinogens include substances such as lysergic acid diethylamide (LSD), phencyclidine (PCP) (angel dust), psilocin (psilocybin), mescaline (peyote), and ketamine (vitamin K). They can be classified into three main types: psychedelics, dissociatives, or deliriants based on purported mechanisms of action. Unlike other psychoactive drugs (e.g., opioids or stimulants), hallucinogens induce changes in perception, thought, emotion, and consciousness. The main difference between a psychedelic versus a dissociative hallucinogen is that acute intoxication with dissociatives results in a more intense detachment from the individual's self and his/her perceived reality. In 2012, there were over one million people aged 12 years or older who were current users of hallucinogens (0.4 %; NSUDH 2013).

104.2.3.1 Neurobiological Mechanisms of Action

Many hallucinogens have chemical structures similar to those of natural catecholamine neurotransmitters such as acetylcholine, serotonin, dopamine, or norepinephrine. Whereas the exact mechanisms remain unclear, psychedelic hallucinogens such as LSD, psilocin, and mescaline appear to exert their effects via agonism of 5-HT_{2A} serotonin receptors, perhaps in conjunction with mGluR2 receptors (González-Maeso et al. 2008) acting within the prefrontal cortex. By comparison, dissociative hallucinogens such as PCP or ketamine appear to exert their effects by temporarily antagonizing glutamatergic NMDA receptors, and deliriants are considered to be anticholinergics. LSD's effects typically begin within 30 min of ingestion and can last up to 12 h.

104.2.3.2 Acute Intoxication

Following acute intoxication, individuals who abuse low-to-moderate doses of LSD may physiologically experience an increase in breathing rate (yet more shallow), dilated pupils, elevated heart rate, hypertension, hyperthermia and diaphoresis, loss of appetite, sleeplessness, and dry mouth. A generalized numbness of the extremities and loss of muscular coordination may occur. At higher doses, blood pressure, pulse rate, and respirations may drop significantly. This may be accompanied by nausea, vomiting, blurred vision, nystagmus, drooling, and/or ataxia. However, the major neurobiological complications following LSD intoxication are psychological. Acute intoxication with LSD may result in neurobehavioral complications such as psychoses, anxiety, panic, and/or hallucinations, wherein transitions between various emotional states are frequent or even sensed simultaneously. LSD may also have dramatic effects on the senses. Acute LSD intoxication can lead to "mash-ups" of colors, smells, sounds, and/or other sensations, which may seem intensified. Sensations may also seem to "cross over." For example, an individual may "hear" colors, while "seeing" sounds. These changes can produce anxiety and ultimately result in panic and terrifying thoughts and feelings of despair or insanity (National Institute on Drug Abuse 2001).

In terms of PCP, intoxicated individuals are often brought to emergency rooms because of overdose or because of the drug's severe untoward psychological effects. Some of the neurobiological complications that PCP abusers may experience include suicidal and/or violent behavior. They can become extremely dangerous to themselves and to others. Acute intoxication with higher doses of PCP may lead to neurobiological severe neurobiological complications such as seizures, coma, and death. Cases of fatal status epilepticus have occasionally been reported (National Institute on Drug Abuse 2001). Because PCP can interact with other CNS depressants such as alcohol and benzodiazepines and enhance sedation, in some instances, acute intoxication with PCP may lead to coma or even death. It is important to note, however, that PCP-induced death is most likely to result from indirect consequences stemming from accidental injury or suicide than it is from a drug-induced physiological consequence.

Neurobiological complications arising from ketamine abuse are similar to those of PCP. Psychologically, acute intoxication with ketamine produces sensations of

detachment from an individual's perceived reality and one's self. There may be wild paranoid delusions, confusion, difficulty concentrating, agitation, alterations in mood, sleep disruptions/nightmares, catatonia, ataxia, and/or deficits in working memory.

104.2.3.3 Complications of Dependence

Repeated abuse of LSD may produce tolerance over time. Toward this, an individual must ingest progressively higher doses of LSD to reach a similar level of acute intoxication that she/he experienced previously. Although LSD does not typically induce addictive-like, compulsive drug-seeking behaviors, chronic abuse of PCP can.

104.2.3.4 Withdrawal

There is no evidence that LSD produces physical withdrawal symptoms when chronic use/abuse of the drug is stopped. However, former LSD users have reported "flashbacks," which have periodically been mistakenly diagnosed as brain tumors or other neurological disorders (National Institute on Drug Abuse 2001). Unlike LSD, the abrupt discontinuation of chronic PCP ingestion can be associated with withdrawal. Symptoms such as memory loss and depression may persist for up to a year after a chronic user stops taking this hallucinogen.

104.2.4 Inhalants

National surveys indicate that nearly 21.7 million Americans aged 12 years and older have used inhalants at least once in their lives. There are four general categories of inhalants: volatile organic solvents, aerosols, gases, and nitrites. Inhalants can be directly insufflated; fumes can be sprayed or deposited inside a plastic/paper sack and "bagged"; gases can be inhaled from balloons; or solvents can be "huffed" directly from an inhalant-soaked rag. Abuse of volatile organic solvents, such as gasoline, butane, glues, paint thinners (e.g., toluene), dry-cleaning fluids, or felt-tip markers, appears to be most prevalent. Volatile organic solvents are highly lipophilic and, therefore, can be neurotoxic.

104.2.4.1 Neurobiological Mechanisms of Action

Mechanisms of action for inhalants appear to be similar to those produced by CNS depressants such as alcohol or barbiturates – except on a shorter time frame. The onset of symptoms for inhalants occurs within seconds. Effects are also short lived and commonly disappear in 30 min or less. Some inhalants such as toluene have been shown to decrease neuronal excitability by acting as an NMDA receptor antagonist and a $GABA_A$-receptor positive allosteric modulator.

104.2.4.2 Acute Intoxication

Acute intoxication with organic solvents such as toluene can produce a variety of feelings including euphoria, exhilaration, or giddiness. Hallucinations, confusion,

nystagmus, drowsiness, ataxia, and temporary memory loss may also occur. This may be followed by nausea and vomiting.

Because intoxication lasts only a few minutes, abusers frequently seek to prolong the high by inhaling repeatedly over the course of several hours (Goforth et al. 2010). This is when the neurobiological complications from inhalant abuse become increasingly apparent. In the short term, many abusers may feel less inhibited and/or out of control. They may experience drowsiness and a lasting headache. Nystagmus, double vision, difficulty enunciating words, ataxia, and progressive cognitive dysfunction can become increasingly evident over time. In some instances, a protracted confusional state may last for several days (Enevoldson 2004).

Upon repeated exposure, inhalant-induced neurobiological complications become increasingly apparent and CNS recovery post abuse may be incomplete. For example, as a result of chronic toluene abuse, there may be cognitive changes, ocular motor abnormalities, and pyramidal features that are unlikely to resolve when drug use has been discontinued. As a result of damage to the myelin sheath, there may also be a loss of coordination and limb spasms. Deterioration may continue for 1–4 months post cessation (Enevoldson 2004). Solvent-induced encephalopathy may also result in cognitive dysfunction, psychiatric symptoms, and cortical and cerebellar brain atrophy (Neiman et al. 2000). Demyelination and gliosis in the cerebral and cerebellar white matter have been observed up to 7 years after chronic abuse and appear to be irreversible (Tamrazi and Almast 2012).

Successive inhalations may lead to death. Acting indirectly, inhalants may lead to death if the substance is inhaled from a bag or abused within a sealed-in area and respiratory depression reaches a point whereby the individual then loses consciousness and suffocates (Neiman et al. 2000). Acting directly, inhalants may lead to death if high concentrations of the substance are sniffed (e.g., using aerosol sprays). This syndrome, known as "sudden sniffing death," can directly lead to heart failure within minutes and result from a single session of inhalant use by an otherwise healthy young person.

It is also important to note that, in addition to the substance of abuse, other chemical ingredients found within the various types of inhalants may produce a variety of other neurobiological complications. Chemical toxicants may result in short-term nausea or vomiting as well as other, more serious long-term neurobiological consequences such as liver and kidney toxicity/damage, hearing loss, and/or bone marrow damage.

104.2.4.3 Complications of Dependence

Addictive-like behavior is not unlikely to develop upon repeated use/abuse of inhalants.

104.2.4.4 Withdrawal

Although rare, compulsive use and a mild withdrawal syndrome can occur with long-term inhalant abuse.

104.2.5 Opioids

Approximately 100 million individuals in the United States have chronic pain. Opioid narcotics are a first line treatment for pain. Prescription opioids include narcotics such as oxycodone (OxyContin), methadone, hydrocodone, and fentanyl. As sales of prescription opioids like these have increased, so too have the complications arising from their improper use and abuse. In 2010, 4.8 % of the US population aged 12 years or older had reported using an opioid pain reliever nonmedically (Paulozzi et al 2011).

Heroin (diacetylmorphine) and morphine differ from the opioids described above. Unlike the synthetic opioids above, heroin and morphine are alkaloid compounds derived from naturally occurring opium. Heroin is mainly used intravenously and, as such, has a greater potential for dependence. When compared to the synthetic opioids such as oxycodone or hydromorphone, former addicts showed a strong preference for heroin and morphine; this finding suggested that heroin and morphine are particularly susceptible to abuse and addiction. Indeed, approximately 23 % of individuals who use heroin once go on to become dependent on it. In 2011, 4.2 million Americans aged 12 years or older (or 1.6 %) had used heroin at least once in their lives.

104.2.5.1 Neurobiological Mechanisms

Opioids act by attaching to three main classes of opiate receptors including mu, delta, and kappa receptors. Heroin can act on all three receptor types. These receptors are found both pre- and postsynaptically on neurons. In general, mu receptors are thought to underlie analgesia by presynaptically enhancing the release of GABA via acute disinhibition. Opioid receptors are located in areas of the CNS such as the nucleus accumbens, amygdala, and cerebral cortex; the spinal cord; as well as the gastrointestinal tract.

104.2.5.2 Acute Intoxication

Euphoric effects of opioids are thought to arise chiefly via activation mu receptors, whereas analgesic effects are thought to arise via activation of the kappa and delta opioid receptors.

Opioids such as oxycodone can induce analgesia, sedation, pruritus, nausea, euphoria, decreased respiration, miosis, and constipation. Some of these effects, such as analgesia, sedation, euphoria, and decreased respiration, tend to diminish as tolerance develops.

At higher doses, opioids can manifest as drowsiness, depress consciousness, an acute change in mental acuity, and/or delirium. Other symptoms include seizures and muscle spasms. Heart rate and breathing can slow or stop resulting in hypoxia or coma. A person experiencing an opioid overdose usually will be nonresponsive. Death may occur. Additional CNS depressants such as alcohol and benzodiazepines are frequently detected in the majority of opioid overdose deaths (National Institute on Drug Abuse 2005; Buttner 2011). One of the only treatments available for opioid overdose is naloxone, an opioid receptor antagonist which can be either injected or intranasally administered in emergency situations.

Heroin does not elevate blood pressure as stimulants do. Accordingly, cerebral infarcts or hemorrhagic stroke is not as likely to result directly from drug-induced effects. However, heroin frequently contains toxic contaminants and is not injected as a pure substance. These impurities can result in an embolus that occludes blood vessels serving the lungs, liver, kidneys, and/or brain, which can result in irreversible necrosis. Indeed, postanoxic encephalopathy is one of the more frequent neurobiological complications of heroin abuse.

Intravenous drug use using nonsterile syringes/equipment increases dramatically the risk of pathogenic infection. Co-occurring infections such human immunodeficiency virus (HIV) and/or hepatitis C (HCV) can produce a set of complex neurobiological complications in and of themselves that can be exacerbated by substance abuse (see Sect. "104.2.8" below).

104.2.5.3 Complications of Dependence

Frequent and regular administration of opioids is associated with tolerance and physical dependence. In terms of heroin, toxic progressive spongiform leukoencephalopathy is evidenced by symmetric white matter degeneration, especially when heroin is smoked (i.e., "chasing the dragon"). Within this white matter, there is a noted activation of microglia (Buttner 2011). In the spinal cord, similar neurobiological complications involving the white matter have been noted. For example, heroin abuse may also produce acute transverse myelitis involving thoracic segments of the spinal cord.

Heroin abuse may sometimes result in permanent peripheral nerve damage. Deep intradermal injections of heroin have produced neuropathies and rhabdomyolysis. Direct trauma surrounding the injection site ("skin popping") is a manifestation of localized edema, which may compress a nerve and have an immediate adverse effect on action potential propagation. If the compression becomes increasingly severe over time, focal demyelination can occur which can be followed by axonal damage and permanent scarring. Compressive neuropathies can occur most commonly in the lateral popliteal and ulnar nerves but also the sciatic nerves. Neuropathies can produce numbness, tremor, or possibly an abnormal gait. Myopathies have similarly thought to arise from drug (or impurity)-induced toxicity and ischemia.

Finally, an increase in the number and distribution of hyperphosphorylated tau-positive neurofibrillary pretangles has been noted in populations of young, chronic heroin abusers. In conjunction with reports of occasional ubiquitin-positive inclusions in neurones of drug abusers, indicate that chronic opioid abuse also leads to drug-related neurodegeneration (Buttner 2011) and brain atrophy (Tamrazi and Almast 2012).

104.2.5.4 Withdrawal

Withdrawal symptoms can include restlessness, muscle and bone pain, insomnia, diarrhea, vomiting, cold flashes with goose bumps ("cold turkey"), and involuntary leg movements. Certain drugs, including heroin, cause strong physical reactions in the body when drug use stops. When a person addicted to heroin stops taking heroin, he or she can experience a variety of symptoms ranging from miosis to

agitation, anxiety, diaphoresis, abdominal cramps, nausea and vomiting, loss of appetite, diarrhea, shivering, sweating, a heightened sensitivity to pain, and/or insomnia.

Typically, opioids should not be used with other substances that depress the CNS. This would include sedatives such as alcohol or benzodiazepines, because these combinations of substances would increase greatly the risk of life-threatening respiratory depression.

104.2.6 Stimulants

Common stimulants include cocaine, amphetamine, methamphetamine, methylenedioxy-methylamphetamine (MDMA), and, increasingly, synthetic cathinones (or "bath salts"). In 2012, there were 1.2 million persons aged 12 or older who were current, nonmedical users of stimulants in 2012 (0.5 %; NSDUH 2013).

104.2.6.1 Cocaine

Cocaine is a water-soluble white salt derived from the leaves of the coca plant. In this form, it can be snorted or injected. Cocaine can also be chemically modified into a free alkaloid and smoked as "crack" cocaine. Cocaine comes in two main forms, a hydrochloride salt or base form. The hydrochloride salt (or powdered) form of cocaine can be either insufflated or dissolved in water and injected. The base form of cocaine is typically formed by adding a solution of baking soda and water into what is referred to "crack" cocaine. In its base form, because of its lower melting point (85–95 °C), crack cocaine is generally smoked. In 2012, there were 1.6 million current cocaine users aged 12 or older, comprising 0.6 % of the population (NSDUH 2013).

104.2.6.2 Amphetamines

Amphetamines are available as capsules, tablets, or fluids. They can be swallowed, crushed and "snorted," injected intravenously, or smoked.

104.2.6.3 Bath Salts

Synthetic cathinones, or "bath salts," are synthetic substances of abuse that chemically resemble cathinone. Cathinone is an amphetamine-like stimulant found naturally in the Khat plant (National Institute of Drug Abuse 2012b). Bath salts can be snorted, ingested orally, or, more rarely, injected (1–3 %) (EMCDDA 2011). Mephedrone and methylone are two of the most common bath salts. Self-reported user surveys in the United Kingdom suggest that approximately 41 % had used mephedrone and 10 % had used methylone in 2012 (Prosser and Nelson 2012). To date, no other known epidemiological prevalence data have been published.

104.2.6.4 MDMA

Also known as ecstasy or molly, MDMA/ecstasy can be ingested orally as a capsule or tablet. Molly (i.e., slang for "molecular") refers to the pure crystalline

encapsulated powder form of the drug. MDMA is commonly taken in combination with other substances of abuse including cocaine, gamma-hydroxybutyric acid, methamphetamine, or ketamine (National Institute on Drug Abuse 2006). NSDUH and MTF data showed generally consistent trends for past-month use of MDMA, with decreases in use from 2002 to the middle of the decade, then increases in use from 2007 to 2010, and declines between 2010 and 2012 (NSDUH 2013).

104.2.6.5 Nicotine

According to the 2010 National Survey on Drug Use and Health, an estimated 69.6 million Americans aged 12 or older reported current use of tobacco – 58.3 million (23.0% of the population) were current cigarette smokers, 13.2 million (5.2%) smoked cigars, 8.9 million (3.5%) used smokeless tobacco, and two million (0.8%) smoked pipes, confirming that tobacco is one of the most widely abused substances in the United States. There are more than 4,000 chemicals found in the smoke of tobacco products. Of these, nicotine, first identified in the early 1800s, is the primary reinforcing component of tobacco.

Neurobiological Mechanisms of Action

Cocaine

Cocaine binds tightly to the dopamine transporter to block its function. Dopamine subsequently accumulates within the synaptic cleft resulting in prolonged and enhanced dopaminergic signaling. Cocaine also reversibly blocks sodium channels. By doing this, it interferes with the propagation of action potentials and acts as a local anesthetic. It also acts as a vasoconstrictor via its inhibition of norepinephrine reuptake in the autonomic nervous system.

Amphetamines

Amphetamines not only inhibit monoamine transporters as does cocaine, but they also stimulate the release of norepinephrine via the inhibition of vesicular monoamine transport, which is responsible for monoamine reuptake into the vesicles for storage from the cytosol. Acting through a variety of mechanisms, amphetamines can also cause release of dopamine from the mesocorticolimbic system and the nigrostriatal dopamine neurons, inhibit metabolic enzymes such as CYP2A6 and MAO, as well as act as a direct agonist on 5-HT receptors.

Bath Salts

Presently, little is known about the pharmacokinetics and pharmacodynamics of bath salts, largely because these substances are frequently abused as a combination of substances and the true contents of these various substances remain obscure. Because of their structural similarity to amphetamines, these compounds are presumed to inhibit monoamine reuptake inhibitors presynaptically and promote the release of norepinephrine, as do amphetamines, and increase the concentration of dopamine, serotonin, and norepinephrine in synapses.

MDMA

MDMA induces the monoamine neurotransmitters to be released from their storage sites in neurons via an inhibition of the vesicular monoamine transporter, which results in increased concentrations of serotonin, norepinephrine, and dopamine in the cytoplasm, resulting in increased neurotransmitter activity. Compared to methamphetamine, however, MDMA causes a surge of serotonin release which is associated with its neurobiological actions/complications (National Institute on Drug Abuse 2013).

Nicotine

The mechanism of action for nicotine dependence includes the activation of ionotropic nicotinic-acetylcholine receptors. Like cocaine, heroin, and marijuana, nicotine increases levels of the neurotransmitter dopamine, which affects the brain pathways that control reward and pleasure by binding nicotinic receptors in the brain. For many tobacco users, long-term brain changes induced by repeated exposure to nicotine can result in addiction, a condition of compulsive drug seeking and use despite known negative consequences associated with its use (e.g., lung cancer). Studies suggest that additional compounds in tobacco smoke, such as acetaldehyde, or perhaps substances of abuse that may be co-ingested (e.g., alcohol) may enhance nicotine's effects on the brain. Upon entering the bloodstream, nicotine immediately stimulates the adrenal glands to release epinephrine (adrenaline) causing a sympathomimetic "fight or flight" response. Epinephrine stimulates the CNS to ultimately increase blood pressure, respiration, and heart rate.

Acute Intoxication

Cocaine

The intense euphoria from snorting cocaine typically lasts 5–10 min. Even though cocaine intoxication generally lasts less than 30 min, it is important to note that its major metabolites (e.g., benzoylecgonine) are broken down and eliminated from the body over a period of several days. Thus, in conjunction with other complicating events, these active metabolites post use may continue to build up and contribute to the manifestation of adverse neurobiological complications several days post use.

Several neurobiological complications may occur as a result of cocaine intoxication. Miosis, hyperthermia, increased heart rate, arrhythmia, hypertension, and vasoconstriction may all occur post use. Seizures may be induced as a result of any combination of cocaine-induced hyperexcitability, cardiovascular dysfunction (arrhythmia), intracranial hemorrhage (hypertension), and/or cerebral ischemia (vasoconstriction). Sudden death may also occur following initial misuse or after repeated abuse. Cocaine-related deaths are often a result of cardiac arrest or seizures followed by respiratory arrest.

Following high doses of cocaine, neurobiological complications may become more severe including bizarre, erratic, and violent behavior. Some cocaine users report feelings of restlessness, irritability, anxiety, panic, paranoia, and 3hallucinations.

Users may also experience involuntary dyskinesias or vertigo, gastrointestinal complications, abdominal pain, and/or nausea (National Institute of Drug Abuse 2010).

Cocaine is the most frequent drug of abuse associated with fatal and nonfatal cerebrovascular events. About 70 % of strokes arising with cocaine-abuse result are hemorrhagic rather than ischemic (Enevoldson 2004). Cocaine-induced hemorrhagic (or ischemic) neurovascular strokes can occur in any brain region. Arteriovenous malformations or aneurysms frequently underlie cocaine-induced hemorrhagic stroke (Buttner 2011). Hemorrhages may be intracerebral, intraventricular, or subarachnoid and generally occur within 1 h post use (Enevoldson 2004).

Cerebral infarction is less common than hemorrhagic stroke but is more commonly associated with smoking crack (Enevoldson 2004). Often these complications present over a more long-term time course such as a headache, encephalopathy, and bilateral clinical/radiological abnormalities.

As with heroin users (see also above), cocaine abusers are at increased risk for contracting such infectious diseases as HIV and/or HCV, not only from stemming shared contaminated needles/drug paraphernalia but also from engaging in risky sexual behaviors as a result of intoxication.

Amphetamines

At higher doses, amphetamines may result in hyperthermia, tachycardia, and/or arrhythmia. An acute agitated state of delirium, paranoia, and hallucinations may also be present. Neurobiological complications may include insomnia, hyperexcitability, aggressive behavior, and/or convulsions. Amphetamine-induced seizures have the potential to subsequently induce cardiovascular failure and death.

When taken nonmedically, amphetamine abuse can produce euphoria, decreased fatigue, heightened arousal, increased libido/fornication, involuntary dyskinesias, irritability, and/or aggressiveness. Appetite may diminish. Mydriasis, hypertension, vasoconstriction, and increased blood glucose may also occur.

Bath Salts

Individuals who abuse bath salts such as mephedrone commonly abuse at least one other substance as well. Recent survey data show that 89 % of mephedrone users reported drinking alcohol, 17 % used cocaine, 23 % used MDMA, 34 % used cannabis, and 24 % used ketamine (EMCDDA 2011). Polysubstance abuse like this is likely to exacerbate and/or increase the likelihood of neurobiological complications associated with bath salt intoxication.

Neurobiological complications commonly associated with mephedrone (poly) intoxication include agitation/aggression, fatigue, impaired attention/poor concentration, increased empathy, talkativeness, and/or an increased urge to move (EMCDDA 2011).

Physiologically, bruxism/teeth grinding (jaw soreness and headache), dizziness, lightheadedness, tremor, and seizures have all been associated with mephedrone intoxication (Prosser and Nelson 2012). Appetitive drive may be significantly

reduced or eliminated. Sweating, headaches, tachycardia, palpitations, nausea, chest pain, and/or increased sexual arousal may also occur (EMCDDA 2011). Adverse events are likely to last 1–2 h post use (Prosser and Nelson 2012).

In terms of medical management, patients with extreme agitation, psychosis, significant tachycardia, hypertension, or seizures following bath salt intoxication should be treated with benzodiazepines to mitigate hyperexcitability and help control convulsive activity (Prosser and Nelson 2012).

MDMA

Acute intoxication with MDMA may lead to a state of confusion, depression, sleep problems, and/or anxiety. The drug's effects last approximately 3–6 h. These neurobiological complications may occur within a few hours post use or present more gradually over a period of days. Heavy users of MDMA may experience long-lasting confusion, depression, sleep abnormalities, and/or problems with attention and memory, although it is possible that some of these effects may be due to the use of other drugs in combination with MDMA (especially marijuana) (National Institute on Drug Abuse 2013).

Physiologically, MDMA produces many of the same effects as other stimulants. These include, for example, increases in heart rate, hypertension, muscle tension, bruxism, nausea, blurred vision, faintness, and/or sweating (National Institute on Drug Abuse 2013).

Hyponatremia is also a commonly reported complication of MDMA use. This is thought to result from several factors including over hydration in the setting of drug-induced secretion of vasopressin (Prosser and Nelson 2012).

MDMA induces a large surge in the release of serotonin. In turn, serotonin triggers the release of the hormones oxytocin and vasopressin, which play important roles in love, trust, sexual arousal, and other social experiences and are likely associated with the characteristic feelings of heightened emotional closeness and increased empathy associated with MDMA abuse. These closeness-promoting effects of MDMA and its use in sexually charged contexts (and especially in combination with sildenafil) may encourage unsafe sex, which is a risk factor for contracting or spreading sexually transmitted infections such as HIV and/or HCV (National Institute on Drug Abuse 2013) (see also Sect. "104.2.8" section below).

Nicotine

Acute intoxication from cigarette smoking or nicotine exposure is rare. Exposure to high doses of nicotine over a short period of time, such as those found in some insecticide sprays, can be extremely toxic, causing vomiting, tremors, convulsions, and death. Nicotine poisoning has been reported from accidental ingestion of insecticides by adults and ingestion of tobacco products by children and pets. Death usually results in a few minutes from respiratory failure caused by paralysis.

Cigarette smoking produces a rapid distribution of nicotine to the brain, with drug levels peaking within 10 s of inhalation. However, the acute effects of nicotine dissipate quickly, as do the associated feelings of reward, which causes the smoker

to continue/increase dosing repeatedly over time to maintain the drug's pleasurable effects, overcome tolerance, and prevent withdrawal.

Complications of Dependence

Cocaine

Because cocaine is highly lipophilic and readily crosses the blood-brain barrier (BBB), it can induce its effects rapidly and has the high potential for dependence. Tolerance can develop. At the same time, abusers can also become more sensitive to cocaine's stimulant effects. The decreased dopaminergic signaling after sustained cocaine abuse may contribute to depressive mood disorders, sensitize the mesodopaminergic circuit toward cocaine's reinforcing effects, and contribute to dependency.

Through an induction of pro-inflammatory cytokines and enhanced leukocyte migration across the brain endothelium, cocaine opens the BBB for HIV invasion and the neurobiological consequences that follow. The presence of acute and chronic BBB breakdown in drug abusers suggests that the brain parenchyma is exposed to unusual quantities of serum proteins, including immunoglobulins, and HIV (Buttner 2011).

As with opioid abuse, imaging data show that chronic cocaine abuse can result in ischemic leukoencephalopathy (Tamrazi and Almast 2012).

Amphetamines

Tolerance can develop rapidly following repeated amphetamine abuse. This can lead to hostility, paranoia, or even psychosis. Amphetamines may also directly induce neurotoxicity. Some studies indicate that neuronal cell loss may be a consequence of excitotoxicity, mitochondrial dysfunction, and/or the subsequent generation of free radicals and nitric oxide (Buttner 2011). Indirect neurotoxicity may result as a consequence of drug-induced damage to astrocytes, axons, and/or the cerebral vasculature. Repeated stimulant abuse appears to decrease basal release of glutamate to stimulate further drug seeking (Goforth et al. 2010) and thereby increase the likelihood for additional stimulant-induced neurobiological complications.

After cocaine, amphetamines are the second leading cause of strokes in persons younger than 45 years (Buttner 2011). In a chronic user, amphetamine-induced strokes usually occur in the first few hours after ingestion. This usually manifests with a headache and progresses into a focal deficit and impaired level of consciousness.

Especially when used chronically and intravenously, amphetamine and methamphetamine are the drugs most commonly associated vasculitis histologically. This, along with a sudden elevation in blood pressure, may result in subarachnoid or intracerebral hemorrhage. Especially in smaller caliber vessels, ischemic infarction may also occur. This could result from the vasoconstrictive effects associated with stimulant use and/or may be an acute hypersensitivity reaction, perhaps, in the case of injectors, due to contaminants of the injection solution (Enevoldson 2004). These complications may result in decreased brain volume. Imaging studies show that there is cerebral atrophy with neuronal damage and glial proliferation following chronic amphetamine abuse (Tamrazi and Almast 2012).

Long-term methamphetamine abuse has many negative health consequences, including extreme weight loss, severe dental problems ("meth mouth"), anxiety, confusion, insomnia, mood disturbances, and violent behavior. Chronic methamphetamine abusers can also display a number of psychotic features, including paranoia, visual and auditory hallucinations, and delusions. Transmission of HIV and hepatitis B or C can also be a consequence of methamphetamine abuse. The intoxicating effects of methamphetamine can also alter judgment and inhibition and lead people to engage in impulsive, unsafe behaviors, including risky sexual behavior.

Bath Salts

A recent survey of 1,506 mephedrone users found that ~50 % consider mephedrone to be addictive (Carhart-Harris et al. 2011). Similar to other stimulants such as cocaine and MDMA, data suggest that mephedrone dependence is associated with psychological, rather than physical, dependency. There is the long-term potential for neurobiological complications as a direct result of acute mephedrone toxicity including status epilepticus-induced cerebral hypoxia (Prosser and Nelson 2012). Despite this, there are no investigations that directly assess chronic neurobiological complications of mephedrone abuse to date.

Preclinical data indicate that repeated administration of mephedrone did not lower striatal dopamine levels or modify the expression of the dopamine transporter. In addition, it was also reported that mephedrone did not cause microglial activation nor did it increase glial fibrillary acidic protein levels in the striatum (Angoa-Pérez et al. 2012).

MDMA

A propensity for MDMA dependence is not clear cut. Some users report symptoms of dependence, including continued use despite knowledge of physical or psychological harm, tolerance (or diminished response), and withdrawal effects. Upon repeated administration, there is evidence that MDMA reduces the concentration of serotonin reuptake transporters in the brain. There are some preclinical and clinical data to indicate that MDMA is associated with dopaminergic and especially serotonergic neurotoxicity, neurodegeneration, and axonal loss, perhaps as a result of increased oxidative stress, excitotoxicity, apoptosis, and/or mitochondrial dysfunction (Buttner 2011).

Nicotine

Cigarette smoking kills an estimated 440,000 US citizens each year – more than alcohol, illegal drug use, homicide, suicide, car accidents, and HIV/AIDS combined. Nicotine dependence linked with cigarette smoking is associated with the inhalation of myriad toxicants (either via primary or secondary smoke) and harms virtually every organ in the body in addition to the CNS. It has been conclusively linked to pneumonia and cataracts and accounts for about one-third of all cancer deaths. In addition to cancer, nicotine dependence linked with smoking also results in lung diseases such as chronic bronchitis and emphysema, and it has been found to

exacerbate asthma symptoms in adults and children. Smoking substantially increases the risk of coronary heart disease, heart attack, vascular disease, cerebrovascular infarction, and brain aneurysm.

Withdrawal

Cocaine

Similar to amphetamines, withdrawal symptoms associated with discontinuation of cocaine use may include lethargy, dysphoria, increased appetite, vivid dreams, disturbed sleep patterns, and/or anxiety.

Amphetamines

Withdrawal from amphetamines does not generally lead to strong physical reactions. Perhaps because associated reactions are not pronounced, symptoms can vary widely across individuals and may include lethargy, dysphoria, increased appetite, vivid dreams, hypersomnia or insomnia, increased or decreased movement, and/or anxiety.

Bath Salts

Reports suggest that there is no reported physical withdrawal syndrome, although psychological dependency is possible.

MDMA

Approximately 60 % of individuals who repeatedly abuse MDMA report withdrawal symptoms. These symptoms include fatigue, depression, diminished appetite, and trouble maintaining concentration (National Institute on Drug Abuse 2006).

Nicotine

Nicotine withdrawal (associated with cigarette smoking) symptoms include irritability, craving, depression, anxiety, cognitive and attention deficits, sleep disturbances, weight gain, and increased appetite. These symptoms onset rapidly within a few hours after the last cigarette, quickly driving people back to tobacco use. Withdrawal symptoms peak within the first few days of smoking cessation but do usually subside within a few weeks post use. For some people, however, symptoms may persist for months.

Although withdrawal is related to the pharmacological effects of nicotine, many cue-induced behavioral factors can also affect the severity of withdrawal symptoms. For some nicotine-dependent people, the feel, smell, and sight of a cigarette and the ritual of obtaining, handling, lighting, and smoking the cigarette are all thought to contribute to the pleasurable effects of smoking and can make withdrawal and/or craving worse. In terms of treatment, nicotine replacement therapies (NRT) such as gum, patches, and inhalers may help alleviate the pharmacological aspects of withdrawal; however, for the aforementioned reasons, cravings often persist making quitting more difficult. Thus, in combination with existing pharmacotherapeutics (e.g., varenicline, NRT, bupropion), behavioral therapies can act to help smokers mitigate environmental triggers of craving and possible relapse.

104.2.7 Sedatives

Sedatives are CNS depressants. Examples include alcohol (ethanol), benzodiazepines such as diazepam (Valium), non-benzodiazepine medications such as zolpidem (Ambien), and barbiturates, such as pentobarbital sodium (Nembutal). Alcohol-use disorders are medical conditions that doctors can diagnose when a patient's drinking causes distress or harm. In the United States, about 18 million people have an alcohol-use disorder, classified as either alcohol dependence – perhaps better known as alcoholism – or alcohol abuse.

104.2.7.1 Neurobiological Mechanisms of Action

Ethanol has multiple diverse actions in the brain. It is known to be positive allosteric modulator of $GABA_A$ receptors, a $5\text{-}HT_3$ receptor agonist, an NMDA receptor antagonist, an AMPA receptor antagonist, a glycine receptor agonist, and an inhibitor of potassium, sodium, and calcium ion channels.

Benzodiazepines bind to the gamma subunit of the postsynaptic $GABA_A$ receptor complex as full agonists to increase the frequency of inhibitory channel opening and to decrease neuronal function. Barbiturates similarly act on the $GABA_A$ receptor but bind to the beta subunit and enhance neuronal inhibition by increasing the mean open time of these ion channels. Barbiturates also inhibit glutamate (AMPA) receptors.

104.2.7.2 Acute Intoxication

Following acute intoxication, sedatives can produce a wide range of effects depending upon dosage consumed. These include induced euphoria, lethargy, ataxia, nystagmus, anxiolysis, confusion, stupor, depressed consciousness, respiratory depression, coma, or even death. Alcohol intoxication can impair significantly cognitive function and motor skills. In addition to hepatic encephalopathy, heavy alcohol ingestion can also affect heart rhythm, can slow respiration, and may even lead to death.

104.2.7.3 Complications of Dependence

Alcohol. Chronic alcohol abuse (i.e., >7 drinks per week for women; >14 drinks per week for men) may produce both structural and functional CNS abnormalities. The pathophysiology of alcohol abuse includes both direct effects on the brain as well as secondary complications arising from liver cirrhosis. In conjunction with nutritional thiamine (vitamin B1) deficiency, chronic alcohol abuse can result in a Wernicke's encephalopathy including ophthalmoplegia, gait disturbances, and a state of confusion; if left untreated, this can lead to Korsakoff psychosis and perhaps eventually death (Tamrazi and Almast 2012). Heavy or chronic use of alcohol may also result in cardiomyopathy, arrhythmias, stroke, high blood pressure, alcoholic hepatitis, fatty liver, fibrosis and cirrhosis, pancreatitis, and increase risk of developing certain cancers, such as cancer of the esophagus, liver, throat, and breast. Chronic consumption of alcohol also suppresses immune system, and chronic drinkers are more liable to infections.

In addition to the well-known tolerance that can develop following alcohol consumption, tolerance can also develop following repeated use or abuse of benzodiazepines and/or barbiturates. Taken orally, these preparations may lead to coma and similar complications to those described from heroin comas, including cardiorespiratory depression (especially after barbiturates), aspiration, anoxic encephalopathy, and peripheral nerve compression syndromes (Enevoldson 2004).

104.2.7.4 Withdrawal

Withdrawal from prolonged barbiturate or alcohol dependence can have life-threatening neurobiological complications. Withdrawal can produce excitotoxicity, irritability, increased tension, diaphoresis, anxiety, panic attack, restlessness, insomnia, tachycardia, delirium tremens, hallucinations, seizures, status epilepticus, or death. Seizures experienced during alcohol abstinence are thought to result from the homeostatic upregulation of NMDA glutamate receptors in the brain. Apoptosis may also occur due to excitotoxicity.

104.2.8 Co-occurring Infections

Injection drug use remains a major risk factor in the acquisition and transmission of viral infections such as HIV and HCV. For example, the hepatitis C virus may remain in the needles, syringes, and/or other drug-injection utensils such as filters, spoons, or even within rinsing liquids. Up to 90 % of HIV-infected injection drug users may also be infected with hepatitis C virus.

Co-occurring infections can each produce their own unique set of neurobiological consequences and may further exacerbate complications produced by substance abuse. HIV may induce mild/moderate motor abnormalities, severe HIV-associated dementia, or neuro-acquired immunodeficiency syndrome (AIDS). HCV infection may cause mild neurocognitive dysfunction or more severe consequences such as hepatic encephalopathy. Because drugs like cocaine and methamphetamine upregulate the chemokine receptors such as CCR5 and downregulate various chemokines that are involved in the viral entry into the immune cells such as microglia, drug abuse is reported to further intensify the neurobiological consequences of viruses like HIV and HCV. Although these complications can also be seen in patients injecting other substances of abuse such as amphetamines or cocaine, they are much more common in heroin abusers who form the vast majority of injection drug users.

Methamphetamine abuse may also worsen the progression of HIV/AIDS and its consequences. Studies of methamphetamine abusers who are HIV positive indicate that HIV causes greater neuronal injury and cognitive impairment for individuals in this group compared with HIV-positive people who do not use the drug.

Long-term infection with both viruses is associated with much more severe neurocognitive consequences. However, clinical management of HIV-associated neurological complications with HIV therapy can improve the

overall cognitive as well as motor performance mono- or dually infected patients, especially when combined with methadone or buprenorphine treatment for substance abuse.

For additional information on co-occurring infections in substance-abusing populations, the reader is directed to a chapter entitled, Chap. 106, "Substance Use and Co-occurring Infections: An Overview," by Khalsa et al. within this book.

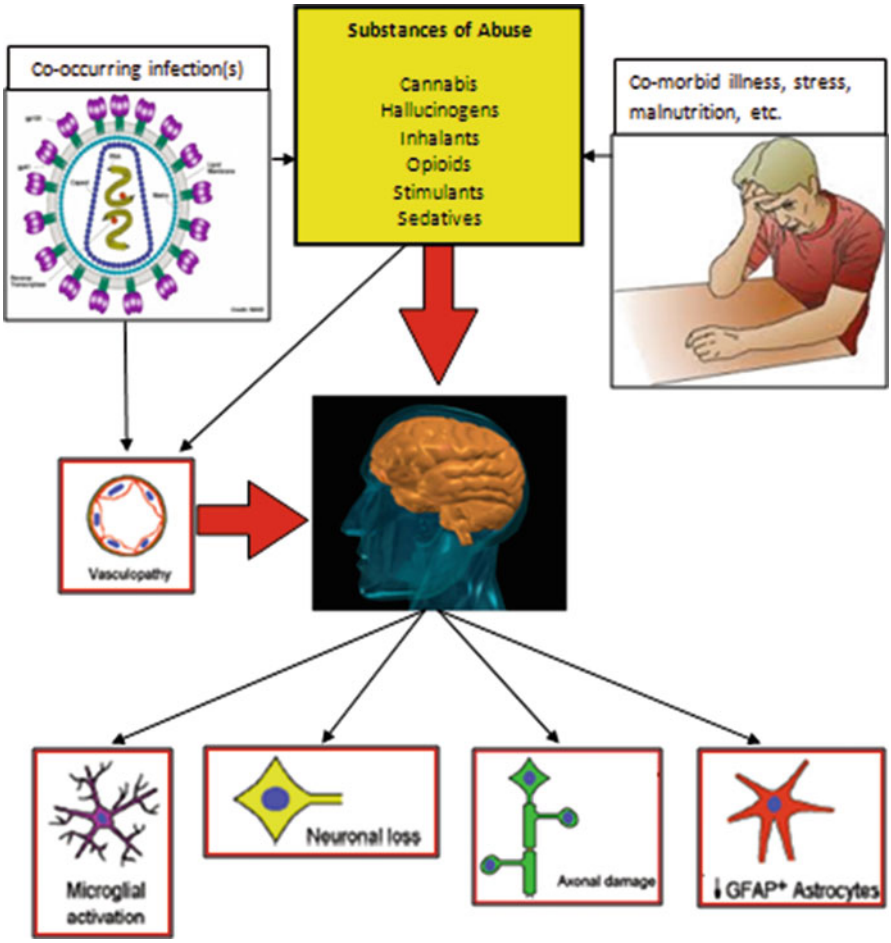

Fig. 104.1 Substance abuse and associated environmental stressors can produce severe negative neurobiological consequences. Whether via a direct or indirect adverse complication arising acutely or subacutely, neuropathological elements such as microglial activation, neuronal cell loss, axonal damage, and/or reduced astrocytes have been noted (see text for details; figure adapted from Buttner 2011)

104.3 Conclusion

Drug abuse is a substantial problem in society today. Substance abuse can result in a complex cascade of toxic, ischemic, and/or hemorrhagic events that directly and indirectly lead to diverse physiological and psychological neurobiological complications (Fig. 104.1). For example, systematic neuropathological studies of polydrug abusers revealed ischemia-independent widespread neuronal loss, a reduction of GFAP-positive astrocytes, an axonal damage with concomitant microglia activation, as well as reactive vasculitis (Buttner 2011). These changes can also influence significantly behavior. Drug abuse can also increase the chances for acquiring/transmitting co-occurring infections that further exacerbate complications arising from abuse.

In the future, imaging modalities such as MRI and computed tomography may aid in the diagnosis and optimal clinical management of drug-related neurobiological complications surrounding SUDs.

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Memory Disorders and Addiction

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Abstract

Memory is a very complex function and it can be affected adversely by almost all substances that are liable to abuse. The totality of memory problems and other cognitive changes will influence profoundly a patient's ability to live and function independently. The effect of substances may be cumulative and can be caused by direct acute or chronic pharmacological action and withdrawal, through secondary mechanisms such as vascular or hepatic damage, and will be also be influenced by the patient's physical, psychiatric, and psychological state. In this chapter the known effects of commonly abused substances are summarized with reference to clinical features and recent brain imaging studies. Memory problems may have a major influence on the ability of patients to interact with treatment, and therefore evidence of memory and other cognitive impairments should be sought for always.

105.1 Introduction

Memory is an essential component of all but the most basic physiological human functions. Any disturbance, be it temporary or permanent, will affect everyday life in one way or another. Memory is also one of the most complex of neurological processes and can be influenced by both mental and physical health disorders, psychological state, and a range of environmental factors including substances. People may complain of a poor memory without there being any objective evidence by formal testing, while others, for example, those with dementia, may deny the existence of memory disorder when it is patently obvious that it is present. Those with memory problems may also demonstrate behavioral and functional dysfunction as well as having psychotic symptoms. Pharmaceutical products, both prescribed by physicians and obtained from other sources and substances used both legally and illegally, can all have potent effects on memory. Their influence can be direct (e.g., benzodiazepines), mediated through associated mechanisms (e.g., thiamine deficiency in alcohol dependence), or through comorbidity (e.g., encephalopathies associated with AIDS or liver disease) or vascular pathologies. As can be seen from Table 105.1, a single substance, e.g., alcohol,

Table 105.1 Factors associated with memory impairment and substance use

Direct intoxication, e.g., benzodiazepines
Chronic use
Withdrawal, e.g., delirium tremens
Associated biochemical abnormalities, e.g., thiamine deficiency
Associated physical illness, e.g., vascular dementia in chronic alcohol abuse
Psychological issues (preceding or consequential)
Comorbid mental illness

can cause memory impairments through a variety of causative and associated mechanisms (see Table 105.1). This chapter comprises a further description of memory and a review of memory problems associated with individual substances with reference to some recent literature.

105.2 Cognitive Aspects of Drug Misuse

The impact of cognitive deficits in drug misuse can have significant effects on both day-to-day function and response to treatment programs (Rogers and Robbins 2001). While memory disorders are most often seen as deficits in the function of memory systems, some theories of addictive behavior focus on the development of pathologically strong memories which influence subsequent drug-seeking behavior (Hyman 2005).

105.2.1 Memory

Memory may be considered under several different headings, for example, short-term (or working memory) as opposed to long-term memory. A classification of memory types is shown in (Table 105.2). An example of short-term memory would be the ability to retain a telephone number read from a directory and then dial that number without having recourse to having to reread that number. Telephone numbers usually have a maximum of seven digits which is the conventional maximum number that can be retained. This type of memory can be tested by digit span tests.

Longer-term memory can be considered as being divided into procedural memory (or implicit memory) and explicit memory. Examples of procedural memory

Table 105.2 Classification of memory disorders

1. Short-term memory/sensory memory
Auditory
Visual
2. Sensory (very short term)
3. Long-term memory
Declarative/explicit
Episodic: autobiographical facts
Semantic: knowledge of the world
Non-declarative/implicit
Procedural skills
Priming: the power of suggestion
Conditioning
Emotional responses
Skeletal musculature
Non associative learning: habituation and sensitization

would include riding a bicycle, driving a car, getting dressed, or using a knife and fork correctly. Of course having an intact memory of how to drive a car or ride a bicycle is only part of the requirements for safety which are integrated with other cognitive skills such as judgement. Explicit memory (memory about facts) can be further subdivided into episodic memory and semantic memory. Episodic memory refers to personal information – what one ate the day before and biographical information about one's family. Semantic memory refers to the meaning of words or, for example, knowing what the capital of France is.

Each of these aspects of memory can be tested separately, but the functional impact depends on the totality of disturbance combined with other cognitive impairments and is modulated by the environment in which the user is placed, e.g., living alone or with somebody else.

The various substances which are liable to misuse can be classified according to type and effect (Table 105.3), and the effects of these substances on memory will be discussed using the following general classification headings:

Table 105.3 Classification of substances

Sedative-hypnotics (central nervous system (CNS) depressants)
Barbiturates
Nonbarbiturate hypnotics
Ethyl alcohol
Benzodiazepines (anxiolytic or antianxiety)
GHB
Narcotic analgesics (opiates)
Opiates
Opiate derivatives
Synthetic opiates
CNS stimulants
Cocaine
Amphetamines
Nicotine
Caffeine
Ecstasy
Psychedelics and hallucinogens
Lysergic acid diethylamide (LSD)
Mescaline (peyote cactus)
Phencyclidine (PCP; "angel dust")
Cannabis
THC; delta-9-tetrahydrocannabinol
Inhalants
Analgesic and anesthetic gases
Glues, solvents, and aerosols

105.2.2 Sedative-Hypnotics (Central Nervous System (CNS) Depressants)

105.2.2.1 Benzodiazepines

Within the normal dose range of prescribed benzodiazepines, an impact on memory can be detected with anterograde amnesia being the most common deficit, elderly subjects being more frequently affected, and the effects being dose related (Curran 1992; Curran et al. 2003). In healthy volunteers who have had therapeutic doses of benzodiazepines, administered effects have been observed on both explicit and implicit measures of memory (Curran and Birch 1991).

The use of benzodiazepines in conjunction with opiate substitution treatments with methadone or buprenorphine has been shown to affect both objective and subjective measures of memory when compared with none drug-using controls (Rapeli et al. 2009).

A review of the effects of benzodiazepines on memory (Beracochea 2006) concluded that while these substances are normally seen as "memory acquisition impairing," most research has not shown evidence of impairment of memory retrieval (retrograde impairment). However, the review highlights the fact that benzodiazepines have been shown to impair other aspects of memory and that impairment of consolidation of memory may result in an apparent retrograde amnesia.

Studies of the impact of benzodiazepines on memory have the potential to be confounded by the underlying psychological and mental health problems for which they are prescribed. A study of the role of benzodiazepines in memory dysfunction in patients with panic disorder was designed to explore this issue and compared a group of patients with panic disorder who were benzodiazepine-free with a group of long-term benzodiazepine users also with panic disorder. The study indicated that panic disorder itself appears to impair nonverbal short-term memory, nonverbal episodic long-term memory and visuo-constructive memory; chronic treatment with benzodiazepines was found to be associated with increased impairment in some aspects of memory (Deckersbach et al. 2011).

105.2.2.2 Narcotic Analgesics (Opiates)

The administration of therapeutic doses of immediate-release opiates in patients receiving palliative care who are treated with sustained-release opiates over a period of time has been shown to produce impairment of both anterograde and retrograde memory (Kamboj et al. 2005). This is in contrast to the findings in healthy volunteers who are administered single oral doses of opiates where only marginal effects on working memory are found (Friswell et al. 2008).

The study of the impact of opiate addiction on memory is complicated by the common pattern of multiple substance misuse including alcohol dependence (Darke et al. 2000; Mintzer and Stitzer 2002), and differentiating the respective contribution of opiates and other substances used by subjects requires complex control measures. The effect on cognitive function of cocaine use in methadone maintenance patients has been studied, and the results indicate that in the absence of

cocaine intoxication, the use of cocaine does not produce any added impairment in cognitive function in methadone maintenance patients (Henry et al. 2012). Studies of neuropsychological function in current methadone patients compared with abstinent heroin users matched for age, education, IQ, employment status, and lifetime drug abuse patterns have shown that methadone consumption alone induces significant cognitive impairment with reduced accuracy of working memory and slower performance on a variety of measures including processing speed and attention (Verdejo et al. 2005).

The neuroanatomical basis of memory deficits in opiate users has been investigated using imaging techniques and demonstrates the key areas which appear to be affected. An fMRI study of opiate-dependent patients compared with healthy controls showed that in tasks which required a high working memory load, the opiate-dependent patients showed hyperactivity in the superior and inferior cerebellum and amygdala and possible hypoactivity in the left prefrontal and medial frontal areas compared with the controls (Marvel et al. 2012). An fMRI imaging study comparing patients treated with methadone or buprenorphine with controls showed altered neuronal activity in the brain areas associated with working memory in those treated with opiates when compared with the controls but found no impairment of visuospatial ability (Bach et al. 2012).

A review of the neuroanatomical basis of working memory found that a number of studies have shown decreased gray matter in the inferior lobes of the cerebellum of a drug- and alcohol-addicted subject (Marvel and Desmond 2010); specifically a study of young lifetime heroin users showed significant decreases in the density of gray matter in prefrontal, temporal, and cingulate areas of heroin-dependent subjects, and the degree of loss of density correlated with the length of time of heroin use (Yuan et al. 2009).

105.2.2.3 Alcohol

The effects of alcohol on memory can be considered within a framework of the nature of the alcohol intake. Conditions such as acute intoxication, hangovers, binge drinking, low to moderate intake, and heavy drinking have all been the subject of research into the cognitive effects of alcohol (Kim et al. 2012).

The acute intoxicant effect of alcohol has been shown to affect both encoding and recall of memories; as alcohol levels increase over a drinking session, encoding is often at a lower alcohol level than recall during the period of intoxication and at a higher level than recall once sober. The effect of state-specific learning is therefore believed to be one of the key factors in observed memory deficits in intoxication. The concept of "alcohol myopia" has been postulated whereby intoxicated subjects encode and recall peripheral information less efficiently than they recall immediate situational cues which are central and subject-centered information (Josephs and Steele 1990; Steele and Josephs 1990). A study of alcohol intoxication and free recall of information in a simulated "real world" situation has shown that the phenomenon of alcohol myopia can be demonstrated (Compo et al. 2011). The impact of alcohol myopia on behavior while intoxicated has been described in risky sexual behavior and may be a more cogent explanation for such

behaviors than disinhibition (MacDonald et al. 2000a, b). Similarly alcohol myopia has been suggested to be a suitable model to partly account for the occurrence of violent behaviors when intoxicated (Giancola et al. 2011). Further research on the concept will be aided by work which has devised a scale to measure alcohol myopia, the Alcohol Myopia Scale (Lac and Berger 2013).

Rapidly increasing levels of alcohol during intoxication are known to precipitate alcohol-induced "blackouts"; this state is characterized by periods of memory loss for events during the drinking period but with retention of consciousness and motor and psychomotor abilities such as conversation and driving during the drinking period (White 2003). This phenomenon does not appear to be state dependent and attempts to induce recall by increasing the alcohol levels to the same point at which the blackout occurred does not result in the retrieval of the lost information (Lisman 1974).

The effect of a hangover, defined as unpleasant symptoms occurring 8-16 h after drinking, on cognition has been explored and indicates that during a hangover state there is impairment of memory (Kim et al. 2003); in particular difficulties with memory retrieval have been identified (Verster et al. 2003). There are considerable methodological difficulties in studying cognitive function during the hangover period; the effects of sleep deprivation, residual alcohol levels, and level and frequency of drinking pattern may all have an independent effect, and research design needs to take account of this (Prat et al. 2008). However, a recent review of the literature on cognitive effects of hangover has concluded that there are four robust studies and four less rigorous but valid studies which indicate specific negative effects of hangover on attention and memory (Ling et al. 2010).

The effects of binge drinking on cognitive function has been the subject of both animal and human research; a review of the literature concluded that binge patterns of drinking can be shown to have effects on both the prefrontal cortex and amygdala resulting in impairment of associative learning. Studies of binge drinking in adolescent subjects using fMRI during memory tasks have shown gender-specific effects on memory tasks with female binge drinkers exhibiting less spatial working memory (SWM) activation than controls, while male binge drinkers showed more SWM activity than controls. The authors suggested that females may be more susceptible to the neurotoxic effects of binge drinking of alcohol during adolescence than males (Squeglia et al. 2011). These gender differences are reflected in the effects of binge drinking on brain morphology in adolescents.

A study using nondrinking controls showed female binge drinkers have greater disruption of cortical brain morphology than male binge drinkers (Squeglia et al. 2012); however, MRI of binge-drinking adolescents has shown reduced cerebellar volumes in male and female binge drinkers compared with controls, and the degree of effect is related to the intensity of the binge-drinking pattern (Lisdahl et al. 2013).

The impact of heavy drinking and alcohol dependence on memory function is well documented, with effects being seen in both short-term and long-term memory and general working memory (Selby and Azrin 1998).

Alcohol-related memory problems are seen with Wernicke-Korsakoff syndrome (WKS); the two clinical presentations of Wernicke's encephalopathy and

Korsakoff's psychosis were originally seen as separate entities but are now known to be a single progressive syndrome. Chronic excess alcohol intake combined with a poor diet will result in a depletion of body store of thiamine. Alcohol blocks the uptake of thiamine from the gut, and this combined with low thiamine content diets can deplete the body store of thiamine in a matter of weeks (Harper 2009). The acute stage of thiamine depletion, whether alcohol related or not, is termed Wernicke's encephalopathy and presents with the distinctive triad of ataxia, mental confusion, and ocular motor disturbance. This can then lead to the end stage of thiamine-deficient brain damage and Korsakoff's psychosis, with irreversible memory changes. If thiamine deficiency is untreated, then up to 20 % of cases will not survive, with the cause of death normally being cardiovascular collapse; aggressive treatment with high dose parenteral thiamine will decrease both the mortality and morbidity arising from thiamine depletion.

The characteristic memory deficits in WKS are related to inability to acquire and recall new information with long-term memory being resistant to thiamine deficiency; imaging studies of patients with acute thiamine deficiency have shown effects in the areas of the third ventricle, the periaqueductal area, the mamillary bodies, and the midbrain which would be consistent with the observed reductions in performance of memory formation (Jung et al. 2012). Some patients with WKS may show the phenomenon known as confabulation; this is seen where patients compensate for the lack of recent memory by filling the gaps in their memory with events which either did not occur or are displaced in time. The exact mechanism responsible for the memory problems seen in WKS is thought to be a complex interaction of alcohol-related damage and thiamine deficiency effects impacting on a variety of cognitive systems which are required for efficient memory storage (Hayes et al. 2012). It has been suggested that the resulting severe anterograde amnesia may not be related directly to alcohol-induced neuronal damage but rather to a disruption of neuronal connections and reduced levels of neurotrophic factors leading to atrophy of isolated and unstimulated neurons (Harper and Matsumoto 2005).

105.2.2.4 CNS Stimulants

Much research on the effects of stimulants on memory has focused on cocaine. Studies of cocaine users who have been abstinent for over 10 days have shown deficits in verbal learning efficiency resulting from poor memory storage, reduced visuospatial abilities, and reduced concentration (Manschreck et al. 1990; Berry et al. 1993; Mittenberg and Motta 1993). Imaging studies during cocaine abstinence using fMRI have shown hypoactivation in brain areas associated with arousal and attention; these areas are associated with dopamine neurotransmission and are located in the cortical and subcortical areas (Tomasi et al. 2007).

The frontoparietal areas of the brain are associated with attention and working memory and have been shown to have reduced activation in fMRI studies in cocaine-dependent subjects; in particular chronic cocaine use is thought to affect the right parietal lobe with reduced performance on verbal working memory tasks (Bustamante et al. 2011).

Other studies have linked fMRI findings with response to treatment in early abstinent cocaine-dependent subjects. When compared with controls, the subjects showed reduced activation in the prefrontal cortex, striatum, and thalamus; these areas are associated with working memory, attention, and vigilance. Low levels of activation in the thalamus pretreatment correlated with poor treatment response (Moeller et al. 2010).

Exposure to stimulants has been shown to affect cognition across age ranges. Prenatal cocaine exposure predicts poorer visual memory at 12 months (Singer et al. 2005); this deficit is not found in prenatal exposure to tobacco or cannabis. Testing of adolescents who were exposed in the prenatal period to cocaine has shown deficits on both incidental face memory and incidental word memory tasks, but no effect on working memory (Betancourt et al. 2011).

The effects of methylenedioxymethamphetamine (MDMA or ecstasy) on memory have been well documented for many years. An impairment of verbal and visual memory was found in studies of abstinent MMDA users when compared with matched controls with the degree of impairment correlating with the amounts and length of time of MMDA use (Bolla et al. 1998). Visuospatial working memory impairment was seen in both current and abstinent MMDA users when compared with controls who had never used the substance (Dafters et al. 2004). The long-term effects of use of MMDA have been studied; a prospective study comparing persistent users of MMDA with less frequent or MMDA naive subjects showed deficits in immediate and delayed verbal recall in the persistent users compared with the naïve and occasional users (Schilt et al. 2007). The use of nonrandomized methods and prospective studies in the study of memory effects of MMDA has been criticized as it may overlook confounding factors such as drug use history and anxiety levels on testing and retesting of memory (Krebs and Johansen 2008, 2012). However, these findings were replicated in a stratified study of MMDA polydrug users which strongly suggested a sustained negative effect of MMDA on verbal memory (Schilt et al. 2008). In addition, studies on middle-aged MMDA polydrug users have shown similar findings to those seen in younger users which were independent of any age-related decline in function (Schilt et al. 2010).

Systematic reviews of the effects of recreational ecstasy have indicated that despite the relatively low quality of some of the research, there is evidence that recreational use of ecstasy is associated with significant deficits in immediate and delayed verbal memory (Rogers et al. 2009) and that there are significant weighted mean effect sizes showing poor performance by ecstasy users on visuospatial memory tasks (Murphy et al. 2012).

105.2.2.5 Nicotine

Perhaps the most commonly used CNS stimulant is nicotine; according to the World Health Organization the global prevalence is 48 % of adult males and 12 % of adult females; this gives an estimated two billion smokers worldwide including child smokers.

The effects of nicotine on performance and memory were the subject of a meta-analysis of all studies published between 1994 and 2008; the authors concluded that there was evidence for positive effects of nicotine on six domains including short-term episodic memory and working memory which were not confounded by withdrawal relief (Heishman et al. 2010). The effect of nicotine on cognitive function has been investigated using fMRI techniques (Kumari et al. 2003). The results which showed activation of a network including frontal and parietal areas are consistent with previous studies which have shown improvements in cognitive function to be related to enhancement of attention and arousal.

Nicotine withdrawal has been shown to produce a decrease in cognitive function including functions such as attention, working memory, and episodic memory (Ashare et al. 2013; Wesnes et al. 2013). Studies of nicotine withdrawal using fMRI techniques have shown significantly reduced activation of the prefrontal cortex and temporal lobes during working memory tasks when treated with a placebo nicotine patch rather than an active patch (Sweet et al. 2010). These effects were more pronounced in subjects aged 50 years and over than in the under 50s suggesting age-related effects may be operating in the magnitude of abstinence effects on cognitive function (Falcone et al. 2013). Treatment of nicotine withdrawal using bupropion has been shown to reduce the level of cognitive impairment on the first day of a quit smoking attempt with improved response times for working memory being seen with bupropion compared with placebo (Perkins et al. 2013). Other studies have shown less clear results with bupropion producing an improvement in working memory during nicotine withdrawal in female subjects but not in males (Ashare and McKee 2012).

105.2.3 Psychedelics and Hallucinogens

The use of so-called psychedelic or hallucinogenic substances such as lysergic acid diethylamine (LSD) and MMDA (see previous section) is not normally associated with the experience of hallucinations except in very high doses. However, the experience of disturbance of perception and cognitive processing is common at low and moderate levels of use (Nichols 2004). Reports of the effects of hallucinogens on memory are mainly confined to those described in the previous section of this chapter regarding the use of MMDA.

With regard to LSD the experience of "flash backs" or reexperiencing of the effects of the use of the drug appears to be a common experience and is classified as hallucinogen persisting perception disorder.

In a review of studies of such experiences (Halpern and Pope 2003), the authors concluded that there were three possible etiological explanations:

(a) They are the result of "heightened awareness of normal visual phenomena."
(b) The result of normal memory with an associated emotional distress.
(c) The result of "lasting memories": resulting from the strong emotional content of the drug experience.

105.2.3.1 Cannabis

Self-reports of the effects of long-term heavy users of cannabis indicate that negative effects of cannabis use on memory are reported in significant numbers of both current (90.5 %, $n = 63$) and former users (88.9 %, $n = 45$) (Gruber et al. 2003) with similar proportions reporting more general effects on cognition.

These self-reported effects on short-term memory have also been documented in web-based studies (Rodgers et al. 2001). A review of the effect of cannabis use on attention, memory, and executive functioning concluded that there is evidence of deficits in all three of these areas from both imaging and neuropsychological studies. Acute effects are seen within 12–24 h of use and are related to cannabis intoxication; longer-term heavier use produces changes which increase in severity over years of use with a good body of evidence showing impairment of recall of word lists and divided attention tasks (Lundqvist 2005). The reversibility of such deficits has been studied using long-term heavy users of cannabis before and after a 28-day washout period and a control group of light users. Heavy users of cannabis showed poorer recall of word lists when compared with light users, but the deficits appeared reversible with no difference between the two groups on retest after the washout period (Pope et al. 2001).

Reviews of studies of the effects of cannabis on neurocognitive functioning covering the period 2001–2007 (Solowij and Battisti 2008) and 2007–2012 (Crane et al. 2013) conclude that acute cannabis effects cover a range of cognitive functions including working memory, attention, and concentration.

There is also sufficient evidence to conclude that cannabis use is associated with impairment of memory beyond the period of the acute intoxicated state.

There are however a number of factors such as age and gender of users, interaction of cannabis with other substances, differences in strength and composition of cannabis used, and length of abstinence from cannabis which may affect the validity of many of the studies with regard to precise conclusions on the effects of longer-term use.

Overall however it would appear that longer-term cannabis use results in impaired attention and concentration, but there is mixed evidence on the effects on working memory.

105.2.3.2 Inhalants

The use of inhalants such as glues, petrol, and other solvents has been shown to have effects on cognition, but many studies have used poly-substance users with resulting lack of clarity as to the exact effect of inhalants (Takagi et al. 2011a, b). Focusing on exposure to specific volatiles has produced clear evidence of impairment of cognitive function and structural brain abnormalities in volatiles such as toluene. A systematic review of both neuropsychology and imaging literature on toluene misuse concluded that there is strong evidence to support an association between this misuse and impairment in a range of cognitive functions including attention, learning and memory, and working memory (Yucel et al. 2008).

Poly-substance users who also use inhalants have been shown to have greater impairment in verbal and nonverbal processing and show more memory problems than those who have not used inhalants (Scott and Scott 2012).

A study of 55 long-term solvent abusers using neuropsychological testing and MRI techniques showed evidence of impairment in working memory and executive functions in the solvent-using group when compared with a control group of users of other drugs. The solvent-using group also showed a higher rate of MRI abnormalities than the other drug users (Rosenberg et al. 2002).

The findings in adolescent inhalant misusers are consistent with studies of occupational exposure both in adolescents and adults (Saddik et al. 2005; Akila et al. 2006) with impairment of working memory and motor dexterity.

105.2.3.3 Cognition Enhancers

The development of a range of substances for treatment of memory problems associated with dementia has produced the potential for misuse of such substances (Lanni et al. 2008), and a black market is reported to already be in existence for purchase of some cognitive-enhancing medications (Jones et al. 2007). The range of putative cognition enhancers is large, and the evidence base for efficacy is poor for many of the substances; there are however trials of the use of some medications in treating substance misusers with memory deficits.

The increasing use of cognitive enhancers by a healthy population for performance improvement is a concern, and their use by students was the subject of a recent review which called for more research on the impact of such drugs in society (Ragan et al. 2013).

A role for cognitive enhancers in the treatment of memory impairment secondary to drug use has been suggested; the aims of such treatment would be to improve function but also to address the circularity of cause and effect in the influence of memory impairment on ability to learn new coping strategies and decrease drug use.

Modafinil is a cognitive enhancer with clinical applications in the treatment of dementia but has also been used to treat long-term, high dose, cocaine users with memory problems. In a clinical trial it was shown to significantly improve two measures of working memory span, but there was no improvement in episodic memory (Kalechstein et al. 2013). Other trials of modafinil using fMRI techniques in cocaine-dependent patients have shown that it modifies the enhanced cue-reactivity to cocaine-related visual stimuli seen in cocaine dependence. The study using a randomized placebo crossover design showed reductions in activity of reward centers and cognitive control areas following dose of modafinil (Goudriaan et al. 2013).

105.2.4 Memory Loss and Engagement with Treatment

The presence of memory loss is an additional factor that is likely to make engagement with treatment more problematic particularly so in those whose lives are already chaotic. Failing to attend for medical appointments and not following instructions about medication are obvious examples. However, differentiating those who do not

want to engage with treatment from those whose memory problems genuinely cause difficulties is often problematic. Some of the strategies to overcome these difficulties in both groups of patients are essentially part of the routine consultation. These include checking with patients that they understand important advice (getting them to repeat it back), providing written information in a form that the patient can understand, and where appropriate, enlisting support from the family. Telephone and SMS reminders are now becoming common practice. Simplifying information to a patient may help people to remember the essentials. The evidence base on improving adherence to treatment in those with memory impairment is limited with most studies being rather small scale. NICE guidance suggests a range of interventions that might be helpful for individuals whose memory problems are such that adherence to treatment is problematic (Nunes et al. 2009).

105.3 Conclusion

The relationship between memory problems and substances is complex. From a clinical perspective, what is required is that clinicians ask patients presenting with substance issues about their memory problems. Informant information is also important. Neuropsychological testing might be helpful. A suggestion of memory loss should lead to the investigation for other cognitive deficits and functional impairments.

Similarly, patients presenting with memory loss should be asked about substance use and again informant information may be useful.

There are few specific pharmacological treatments for memory loss, and the management plan should be focused on treatment of the underlying substance problem and treatment of physical and psychiatric comorbidities and psychosocial support.

105.4 Case Vignettes

105.4.1 Patient 1. Female Aged 63

Presentation: Referred to a memory clinic by family physician. History of 6 months of declining memory. She forgets appointments and dates. Her husband has to supervise medication and assist with cooking. Her husband has taken over domestic finance. One episode of not recognizing daughter. Four blackouts but none for past year. Alcohol history: Drinks 8 UK units a day for several years. Medication includes thiamine and vitamin B complex. Mini-mental state score 28/30.

Assessment: Typical history of Alzheimer's disease but MMSE score higher than would be expected for the degree of impairment. Drinking above safe limits.

Progress: No change in drinking habits. Admission to hospital because of gastritis/hematemesis. Abnormal liver function tests. Acknowledges risk of alcohol but declines referral to alcohol treatment service.

Issues: In view of the clinical history which suggests Alzheimer's disease, should this patient be prescribed cholinesterase inhibitors? Is it desirable in patients such as this to differentiate between alcohol-related dementia and Alzheimer's disease? Should memory clinics, primarily designed for older people with degenerative dementia, also provide alcohol treatment services?

105.4.2 Patient 2. Female Aged 75

Presentation: Progressive memory loss over 12 years, worse over the previous year. Sometimes disorientated in time but not in place. Tendency to be repetitive in speech. She mixes up her children's names. She performs most basic activities of daily living well but needs occasional help from her family. She drinks two glasses of wine each evening with her meal (5 UK units). Her mini-mental state examination score was 16/30.

Past medical history: Delirium with urinary tract infection, minor strokes.

Assessment: Thought to have a mixed dementia. No recognized clinical features of vascular dementia but CT scan showed vascular disease. Drinking above safe limits of alcohol but not excessively so.

Issues: On initial assessment: What advice should be given about alcohol consumption in view of suggested protective effect on vascular disease?

Progress: Her condition deteriorated and 6 months later she was drinking two bottles of wine a day. She completely denies any issues with alcohol or memory. She is supported by her son at home who visits three times a day.

Issues at this time: Is any therapeutic intervention likely to be of benefit? In retrospect should a more aggressive approach to trying to reduce alcohol consumption at initial presentation been made?

105.4.3 Patient 3. Female Aged 63

Presentation: A 63-year-old woman taken on for treatment after she presented with distressing tactile and auditory hallucinations. She was a regular cannabis user, and a week prior to the sudden onset of her psychotic symptoms, a new GP had significantly and suddenly reduced the woman's longstanding diazepam prescription from 30 to 5 mg daily. On admission her husband reported that he noticed that her memory was deteriorating and that she had been using cannabis more heavily than previously.

Assessment: A full assessment of her mental and physical state following withdrawal from cannabis and benzodiazepines is needed so as to differentiate the possibilities of her condition at presentation, i.e., diazepam withdrawal, or cannabis-induced psychosis or other possibilities for a new presentation at this time of life was a new onset organic cause and nothing to do with her substance use.

Progress: The patient was detoxified from diazepam but refused to stop cannabis completely.

Her psychotic symptoms subsided and although her memory improved considerably she still had some cognitive dysfunction.

Issues: Continued counseling for cannabis use, and assessment for depression and anxiety, for which she had been treated initially, and keeping an eye on the development of an organic cause for memory dysfunction, would be a way forward.

105.4.4 Patient 4. Male Aged 60

Presentation: A 60-year-old man presented to the drug service with positive urine test for opiates.

He was shocked as were the staff. He had been stable on a dose of 50 mls methadone for 10 years. He had begun a prescription when he had become dependent on heroin following the need for pain relief for back ache. His partner had recently died and he felt low and lost. He also complained of difficulty in concentration. When probed as to whether he had taken any new medications for any reason, he volunteered that he had taken what he thought was some aspirin which he had found in the house.

Assessment: The urine sample was sent for toxicological analysis where codeine and benzodiazepines were found. He brought in some of the tablets which were analyzed and were indeed a combination of codeine and aspirin. He stopped using these and he was advised to take them to a pharmacy for disposal.

Issues: Comprehensive assessment of the mental and physical state as well as more detail about other prescription or over the counter substances is essential.

The possibility of drug interaction and unsuspected drug interaction due to patient ignorance.

Progress: Following some bereavement counseling and abstinence from all other medications, the patient improved and wanted to start a methadone reduction program.

105.4.5 Patient 5. Male Aged 62

Presentation: A 62-year-old man presented to the emergency clinic requesting detoxification. He said that he had forgotten to collect his grandchildren from school one day and that he now wanted to be drug-free so that he could continue his role in their care.

At the time of presentation he was drinking alcohol, using benzodiazepines, taking cocaine occasionally, and topping up his methadone prescription with street opiates. He lived with his partner and had a central role in the care of his two grandchildren.

He had a longstanding history of substance misuse.

He had first tasted alcohol at the age of 5 years and started drinking regularly at 12 years. He had tried almost every substance, including solvents, amphetamines, ecstasy, magic mushrooms, and heroin. He had been in custody for three periods because of theft, burglary, and shoplifting offences, committed to fund drugs or to maintain basic living needs.

During this initial presentation he appeared not to be able to give a coherent history about his drug-taking career.

Assessment: Further detailed assessment of cognition is required in relation to corroboration of his substance use at the present time and in the past.

He is on numerous drugs which might have an impact on his cognition, e.g., benzodiazepines, cocaine, and methadone.

This has to be separated if possible from other mental and physical health problems which might interfere with attention and concentration.

Issues: This is clearly complex so ideally admission for detoxification and regular reassessment is needed following stabilization of substitution therapy and detoxification from alcohol and benzodiazepines. The patient needs to be informed about the effects on memory of all the drugs he is taking as he may not realize what the impact may be. The care of his grandchildren needs to be reconsidered and reviewed since the episode may simply have been a "one off" or have more serious implications. This may help him resolve to reduce or stop drug use.

Progress: The patient was admitted and detoxified. He was reassessed regularly but continued to use a range of substances albeit erratically.

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Substance Use and Co-Occurring Infections: An Overview

106

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Contents

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Abstract

Substance use and co-occurring infections are two of the major health issues in the world today. Both cause serious health complications involving almost every physiological system. Most notably, in substance users, human immunodeficiency virus (HIV) and/or hepatitis C virus (HCV) are common co-occurring infections. These infections result in immunological impairment and a related enhancement in the acquisition/transmission of other opportunistic infections ([OIs] such as tuberculosis [TB], streptococcus, staphylococcus). There are also neuropsychiatric complications and consequential liver damage frequently associated with chronic HCV infection. Research suggests that clinical management of substance users with co-occurring infections is feasible. In addition to preventative measures to reduce substance use or infective complications such as education, prodromal diagnosis, medical therapy, and close monitoring for medication adherence to treatment regimens in substance users is likely to be significantly effective at reducing the global health care burden in this highly vulnerable population.

106.1 Introduction

Substance use and co-occurring infections and associated morbidity and mortality are among the most significant health problems that the world faces today. Although numerous viral and bacterial infections occur in substance-using individuals, in this chapter, we review in depth current research on health consequences associated with viral infections such as human immunodeficiency virus (HIV) and hepatitis C virus (HCV), as well as briefly review sexually transmitted infections (STIs), TB, and fungal and parasitic infections. We also summarize currently available therapeutic modalities for the treatment of viral infections in the substance-using population. Due to space constraints, the reader is also directed to the websites of www.who.org, www.unaids.org, www.cdc.gov, and www.drugabuse.gov for additional current information on statistics for substance use and infections.

It is estimated that 153–300 million people abuse illegal drugs regularly worldwide (World Drug Report 2012). In the USA alone, it is estimated that 22.5 million Americans 12 years of age and older (8.7 % of the population) have used at least one illegal drug (e.g., cocaine, heroin, cannabis) (SAMHSA 2013) during the month prior to the survey interview. In addition to substance use, more than half of the world population is currently infected with one or more infections. There are an estimated two billion people infected with the hepatitis B virus, of whom more than 350 million are chronically infected; and of these subjects chronically infected with HBV, an estimated 500,000–700,000 people die each year. There are nearly 2.3 billion people infected with *Mycobacterium tuberculosis* (TB), of which nine million people go on to develop TB disease each year. This ultimately results in about 1.4–2 million TB-induced deaths annually. There are an estimated 170–200 million people chronically infected with the hepatitis C virus (HCV), of which more than 350,000 people die each year from HCV-related liver disease. And since 1981, when acquired immune deficiency syndrome (AIDS) was first described, an estimated 60 million people have contracted the

human immunodeficiency virus (HIV), nearly 30 million have died of HIV-related causes, and approximately 34 million people currently live with the infection. An estimated 23.5 million (69 % of all people living with HIV) live in sub-Saharan Africa including 91 % of the world's HIV-positive children. About 2.5 million new cases of HIV infection are reported each year (United Nations AIDS 2012).

Globally around 16 million people inject drugs, and three million of them are living with HIV. On average 10 % of new HIV infections are caused by injection drug use. In parts of Eastern Europe and Central Asia, over 80 % of all HIV infections are related to drug use (WHO 2010). Indeed, according to the Centers for Disease Control and Prevention (CDC), drug use remains the third most frequently reported risk factor for HIV infection in the USA after male-to-male sexual contact or high-risk heterosexual contact. Men who have sex with men (MSMs) around the world have higher HIV prevalence rates than the general population of reproductive-aged adults, with highest rates in sub-Saharan Africa and the Caribbean regions. Pooled HIV prevalence ranges from 3 % in the Middle East and southeast North Africa region to 15.4 % in North America and 25.4 % in the Caribbean. It is important to note that young MSM in the USA and elsewhere have the highest rates of HIV infections. But they are also the least likely to be in HIV care. Further, the high prevalence of HIV among MSMs also drives new infections and increases the lifetime likelihood of HIV acquisition among its members (Beyrer et al. 2012). Although a significant portion of HIV-infected MSMs do not enter into HIV care and better intervention programs are needed to engage them into HIV care, MSMs can be successfully treated with the currently available behavioral and antiretroviral therapeutic modalities combined with addiction therapy for HIV-infected drug-using MSMs (The Lancet 2012: http://www.amfar.org/uploadedFiles/_amfarorg/On_the_Hill/SummaryPtsLancet2012.pdf).

Other than injection drug use as a risk factor for exposure to HIV, ongoing substance use, correlates of the lifestyles associated with substance use, and issues of access and adherence to treatments for substance use and its associated medical consequences represent just some of the ways in which drug-related factors interact to affect the onset and progression of HIV/AIDS.

In terms of HCV infection, of the estimated 170–200 million people infected with HCV worldwide, nearly 1 % of the US population is currently infected with HCV. An estimated 80–90 % of HIV-infected injection drug users (IDUs) are also coinfected with HCV that may result in liver cancer and death. Approximately one million people worldwide die each year from liver disease/cancer. Injection drug use accounts for 60 % and 25 % of new HCV and HIV cases, respectively (Sullivan and Fiellin 2004). Injection drug use is also a major risk factor for HCV/HIV coinfection that can significantly impact the transmission and progression of either disease. Although both HCV and HIV infections share common routes of transmission and risk factors, sexual transmission of HCV is low among non-IDUs (Hammer et al. 2003). An estimated 80–90 % of HIV-infected IDUs are also coinfected with HCV that may result in liver cancer and death. Approximately one million people worldwide die each year from liver disease/cancer. Among IDUs worldwide, the incidence and prevalence of HCV infection are

50–90 % and 10–30 % per year, respectively (Hagan and Des Jarlais 2000). More recently, in an emerging epidemic in the USA, injection drug use has played a major role in the transmission of HCV infection among 18–25-year-old young adults who switched from prescription drug use to injecting drugs (Valdiserri et al. 2014; CDC 2013).

106.2 Substance Use and Co-occurring Infections

106.2.1 Human Immunodeficiency Virus (HIV)

HIV is a blood-borne retrovirus and infects CD4 T-cell lymphocytes and macrophages causing profound immunosuppression. In some cases, it eventually may develop into full-blown AIDS (CDC 2013). The course of HIV infection and development of AIDS can be complicated by a variety of metabolic and endocrine abnormalities secondary to the direct toxic effects. These result in viral infection, opportunistic infections (OIs), neoplasms, and complications of antiretroviral therapy. In acute infection, 40–90 % of patients exhibit transient symptoms. In general, the time from initial exposure to symptoms, such as flu-like syndrome consisting of fever, fatigue, and pharyngitis, is about 2–6 weeks; and the mean duration of symptoms lasts 1–2 weeks (Quinn 1997). Almost all patients seroconvert in less than 6 months. There are several factors that can speed up this process. Seroconversion may be accelerated by the individual's genotype, risky sexual behaviors, illicit drug use, and/or the presence of other OIs. Other clinical features of acute infection can include decreased CD4 T-cell lymphocytes and increased viral load and progression to AIDS. In chronic HIV infection, the rate of progression to AIDS is variable and dependent on several factors such as the use of illicit drugs, OIs, and adherence to antiretroviral therapy (ART). Without access and adherence to treatment, the median time from initial infection to AIDS is about 8–10 years (Vergis and Mellors 2000). In terms of diagnosis, the viral load and CD4 cell count are used to assess the stage of disease progression and evaluate the treatment efficacy. HIV infection does not progress to AIDS in about 5 % of individuals. Known as the long-term nonprogressors, these individuals present with a low viral load burden, strong virus-specific immune response, and moderate viral attenuation (Cao et al. 1995).

106.2.1.1 HIV and Substance Use

The combination of substance use and co-occurring infections is associated with more serious adverse health consequences than either drug abuse or an infection alone. These consequences may include increased risk of immune dysfunction, cardiometabolic diseases, persistent dysregulated chronic inflammation, tissue fibrosis, increased vulnerability to infections, and premature aging. Thus, prevention and clinical management of dually infected drug-addicted patients also need to be innovative and effective. Treatment of infectious diseases in substance-using patients requires a multipronged therapeutic approach that addresses the type of infection and psychiatric, medical, legal, and social consequences of addiction (Volkow and Li 2005).

A good example of this is methadone. Since the 1960s, methadone has been effectively used for the treatment of opiate addiction and among HIV-infected heroin-using populations following the emergence of the HIV pandemic in the 1980s. Methadone treatment decreases opiate use as well as needle sharing among opiate addicts and reduces the number of multiple sex partners and the practice of exchanging sex for drugs or money (Meandzija et al. 1994). In addition, there is also evidence that methadone therapy lowers the incidence and prevalence of HIV infection among opiate injectors (Metzger et al. 1993).

106.2.1.2 Treatment of HIV/AIDS in Substance Users

Interventions for HIV/AIDS among substance users consist of preventive measures, lifestyle and behavioral changes, and the use of pharmacotherapies. Firstly, prevention must be targeted to slow the spread of infection by the use of sterile injection equipment and safer sexual practices (e.g., use of condoms), as well as discouraging the use of illegal drugs. Treatment of HIV/AIDS, consisting of postexposure prophylaxis of acute infection, has been proven safe and effective for IDUs in methadone treatment programs and to further prevent the spread of infection (O'Connor 2000). Treatment for substance use disorders, for example, with methadone or buprenorphine, further improves adherence to antiretroviral therapy and prevention of development of antiretroviral (ARV) drug resistance. Treatment of HIV during its acute phase produces a strong HIV-specific response of CD4 cells and undetectable virus. These patients have fewer OIs and mitigated disease progression to AIDS (Berrey et al. 2001). Since the approval of the first ARV medication, zidovudine [AZT] in 1987, several new, pharmacologic agents have been approved for the treatment of HIV/AIDS. In general, these ARVs fall into six broad categories with disparate mechanisms of action (De Clercq 2009): nucleoside reverse transcriptase inhibitors (NRTIs), nucleotide reverse transcriptase inhibitors (NtRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), cell entry inhibitor (fusion inhibitor [FI] that binds selectively and inhibits fusion of the virus to the CD4 cell, Lalezari et al. 2003), co-receptor inhibitor (CRI), and integrase inhibitor (INI) (See Table 106.1).

The best virologic response is seen when three or more drugs, known as highly active antiretroviral therapy (HAART), are used to treat HIV/AIDS (Baxter et al. 2000). Briefly, HAART consists of two NRTIs combined with either an NNRTI or a PI (USPHS Kaiser Guidelines 2003) or any of the new inhibitors. Most recently, a 5-drug combination has been reported to cut down even the viral reservoir (Wolf et al. 2013). The goals of HAART include long-standing viral suppression, restoration and preservation of immunological function, improved quality of life, and decreased HIV-related morbidity and mortality. The risk for OIs such as *Pneumocystis carinii*, *Toxoplasmosis gondii*, or *Mycobacterium avium complex* increases as the CD4 count declines below 200/mm^3, 100/mm^3, or 50/mm^3, respectively, and that is when the primary and secondary prophylaxis should be instituted. HAART has significantly reduced the morbidity, including the AIDS-defining illnesses and mortality of HIV/AIDS (Pallela et al. 1998). The effectiveness of therapy is impacted by adherence, safe sexual practices, injection of psychoactive drugs, and any of the many side

Table 106.1 Drugs used in the treatment of HIV infection

Brand name	Generic names(s)	Manufacturer name
Multi-class combination products		
Atripla	Efavirenz, emtricitabine, and tenofovir disoproxil fumarate	Bristol-Myers Squibb and Gilead Sciences
Nucleoside reverse transcriptase inhibitors (NRTIs)		
Combivir	Lamivudine and zidovudine	GlaxoSmithKline
Emtriva	Emtricitabine, FTC	Gilead Sciences
Epivir	Lamivudine, 3TC	GlaxoSmithKline
Epzicom	Abacavir and lamivudine	GlaxoSmithKline
Hivid	Zalcitabine, dideoxycytidine, ddC	Hoffmann-La Roche
Retrovir	Zidovudine, azidothymidine, AZT, ZDV	GlaxoSmithKline
Trizivir	Abacavir, zidovudine, and lamivudine	GlaxoSmithKline
Truvada	Tenofovir disoproxil fumarate and emtricitabine	Gilead Sciences, Inc.
Videx EC	Enteric-coated didanosine, ddI EC	Bristol-Myers Squibb
Videx	Didanosine, dideoxyinosine, ddI	Bristol-Myers Squibb
Viread	Tenofovir disoproxil fumarate, TDF	Gilead
Zerit	Stavudine, d4T	Bristol-Myers Squibb
Ziagen	Abacavir sulfate, ABC	GlaxoSmithKline
Nonnucleoside reverse transcriptase inhibitors (NNRTIs)		
Rescriptor	Delavirdine, DLV	Pfizer
Sustiva	Efavirenz, EFV	Bristol-Myers Squibb
Viramune	Nevirapine, NVP	Boehringer Ingelheim
Protease inhibitors (PIs)		
Agenerase	Amprenavir, APV	GlaxoSmithKline
Aptivus	Tipranavir, TPV	Boehringer Ingelheim
Crixivan	Indinavir, IDV	Merck
Fortovase	Saquinavir (no longer marketed)	Hoffmann-La Roche
Invirase	Saquinavir mesylate, SQV	Hoffmann-La Roche
Kaletra	Lopinavir and ritonavir, LPV/RTV	Abbott Laboratories
Lexiva	Fosamprenavir Calcium, FOS-APV	GlaxoSmithKline
Norvir	Ritonavir, RTV	Abbott Laboratories
Prezista	Darunavir	Tibotec, Inc.
Reyataz	Atazanavir sulfate, ATV	Bristol-Myers Squibb
Viracept	Nelfinavir mesylate, NFV	Agouron Pharmaceuticals
Fusion inhibitors		
Fuzeon	Enfuvirtide, T-20	Hoffmann-La Roche & Trimeris
Co-receptor inhibitors		
Selzentry	Maraviroc	Pfizer
Integrase inhibitors		
Isentress	Raltegravir	Merck

Table 106.2 Antiretroviral agents in development

Therapeutic class	Mechanism of action
Maturation inhibitors	Prevent the development of HIV's internal structures
Assembly and budding inhibitors	Interfere with the final stage of the HIV life cycle
Zinc finger inhibitors	Break apart structures holding HIV's inner core together
Antisense drugs	Lock onto the virus to prevent it from functioning
Cellular metabolism modulators	Interfere with HIV's ability to self-replicate
Immune therapies	Help the body defend against HIV
Gene therapies	Block HIV replication by producing immune cells that are genetically resistant to HIV infection
Variety of Immune modulators (e.g., cytokines)	Increase the host immune system's response to HIV

effects. These may include ART hypersensitivity, mitochondrial toxicity (hepatic steatosis, lactic acidosis), neuropsychiatric symptoms, metabolic (lipid) abnormalities, cardiovascular complications, and drug-drug interactions. Still to overcome some of the adverse drug effects associated with the current HAART, newer agents continue to be developed (see Table 106.2).

Treatment of HIV infection in IDUs generally poses a significant challenge to clinicians since patients adhere poorly due to reported poor adherence to treatment regimens, engage in risky and unsafe sexual behaviors, and continue injection drug use. However, studies show that HAART therapy is effective among drug abusers who are successfully enrolled into drug treatment programs, and thus substance use treatment must become an integral part of HIV management (O'Connor et al. 1994) where the compliance to treatment is also significant. One of the complications that can occur in this population is pharmacokinetic drug-drug interactions between antiretroviral medications and opioid agonists, such as methadone. Methadone increases the blood levels of oral and intravenous zidovudine [AZT] as well as decreasing its clearance but decreases the blood levels of other NRTIs – didanosine and stavudine – suggesting that higher doses of these medications might be necessary in patients in methadone treatment. NRTIs themselves do not alter the levels of methadone, while NNRTIs that induce cytochrome P450 enzymes significantly decrease blood methadone levels, requiring the administration of supplemental doses to prevent opiate withdrawal. The coadministration of methadone, PI, and two other NRTIs leads to increased metabolism of methadone requiring methadone dose adjustment, whereas the coadministration of buprenorphine and AZT has no significant effect on any medication, viral load, or CD4 count in HIV/AIDS patients. Pharmacokinetic/pharmacodynamic drug interactions between medications for the treatment of addiction and HIV have been recently covered by McCance-Katz and colleagues in a special supplement of American Journal of Addiction (McCance-Katz et al. 2010; Khalsa and Elkashef 2010).

106.2.2 Hepatitis C Virus

Hepatitis C infection is the most common chronic blood-borne infection. As mentioned above, it affects an estimated 170–200 million people worldwide. An estimated 3.2 million persons are chronically infected in the USA (CDC 2013. Sixty to 70 % of persons newly infected with HCV typically are usually asymptomatic or have a mild clinical illness (acute infection phase). HCV RNA can be detected in blood within 1–3 weeks after exposure. The average time from exposure to antibody to HCV (anti-HCV) seroconversion is 8–9 weeks, whereas antibodies to HCV can be detected in >97 % of persons within 6 months after exposure. Mild clinical illness symptoms may include malaise, nausea, right upper quadrant pain, and jaundice. During the chronic phase of HCV infection that may last several decades, symptoms may include nausea, anorexia, myalgia, and arthralgia, with fatigue being the most common complaint. Alcohol use and advanced age accelerate the disease progression, especially among men. Approximately 20 % of these chronic patients will develop liver cirrhosis within 20 years, and 1–5 % of them will die from HCV-related liver cancer. Chronic HCV infection develops in 70–85 % of HCV-infected persons; 60–70 % of chronically infected persons have evidence of active liver disease. The majority of infected persons might not be aware of their infection because they are not clinically ill. However, infected persons serve as a source of transmission to others and are at risk for chronic liver disease or other HCV-related chronic diseases decades after infection. Chronic HCV infection is also associated with the development of diabetes mellitus among IDUs as well as non-substance-using populations. Further, gender (being male), poor immune system (i.e., lowest level of CD4+ lymphocytes), and highest viral load are all significantly correlated with liver disease progression (Rubio Caballero et al. 2004). Sexual and mother-to-child transmission of HCV, although rare, may occur during the pre- or postpartum period up to the age of 1 year via breast feeding or nosocomial transmission (Serfaty 1999). In Australia, HCV infection through prenatal transmission has been reported in children. Although HCV infection was largely asymptomatic, more than half the children had biochemical evidence of ongoing liver damage. Due to the chronicity of HCV infection and the long-term risks of liver cirrhosis and hepatocellular carcinoma, children with HCV infection represent a high-risk group worthy of routine follow-up (Karim et al. 2000).

HCV infection may resolve spontaneously in about 15–25 % of the infected people (although different studies report viral clearance rates of 10–50 %); it may persist without complications or become chronic in 75–85 % causing end-stage liver disease (ESLD), hepatic cancer, and death. Viral clearance occurs more often in Caucasians and those not infected with HIV than among people of African descent. The latter population clears the virus slowly and responds less favorably to treatment due to the absence of an IL28B cc allele as compared to the people of Caucasian descent (Duggal et al. 2013). The risk of ESLD is also higher for older persons and who consume more than 260 g of alcohol per week. Marijuana use is also associated with rapid progression of liver disease in HCV-infected subjects.

Although HCV infection could be self-limiting or associated with ESLD, the majority of adults have persistent viremia without clinically demonstrable liver disease. HCV viremia and inflammation are temporarily suppressed by interferon, but the relevance of these surrogate endpoints to progression of liver disease, and survival still needs to be assessed (Prestileo et al. 2000).

There are no prophylactic treatments (e.g., a vaccine) available for preventing HCV infection. Therefore, the medical management of HCV infection to date has focused upon primary prevention and pharmacotherapy. Primary prevention efforts include (a) improving the safety standards surrounding blood supply, (b) safe injection practices in health care, (c) fostering safe injection practices in other settings (e.g., needle distribution programs), (d) decreasing the number of people who initiate injection drug use (Shepard et al. 2005), (e) promoting lifestyle/behavioral changes (e.g., avoiding/minimizing alcohol use, eliminating hepatotoxic medications, avoiding high-risk sexual practices), (f) aggressive pretreatment of opportunistic co-occurring infections (e.g., TB) that are known to accelerate the progression of HCV disease, and (g) treatment with pharmacological agents during acute and chronic stages of infection. The issues of HCV prevention, care, and treatment have been addressed by Ward et al. (2012). The factors predictive of HCV seroconversion among IDUs are the exchange of syringes and cotton sharing (Lucidarme et al. 2004).

Rapid progress in the treatment of HCV infection has led to highly successful therapies that lead to viral eradication and sustained viral response in more than 50 % of patients. Nevertheless, subpopulations like HCV-/HIV-coinfected subjects, alcohol abusers, and HCV-infected African-Americans have reduced rates of treatment response. The use of peginterferon in conjunction with ribavirin improves response rates, but does not fully ameliorate the response deficit relative to patients enrolled in typical drug registration clinical trials (Sherman 2003). Incidentally, high viral load (HCV RNA levels) is associated with a poor response to treatment of chronic HCV and vice versa, and factors such as older age, alcohol use, and coinfection with HIV are predictors of higher viral load among drug users. More recently, two antiviral protease inhibitors – boceprevir and telaprevir – have been approved for treating HCV infection. Although both agents induce a high sustained virologic response (SVR), these must be administered in combination with peginterferon, which is associated with serious side effects. New antivirals that need NOT be coadministered with peginterferon are currently in various stages of development and should be available within the next few years for treating acute or chronic HCV infection.

106.2.2.1 HCV and Substance Use

In the USA, the prevalence of HCV infection in substance users has been reported to approximate 35 % (Hwang et al. 2000). In Japan, it is around 54 % among methamphetamine users, probably because of a high rate of needle and/or syringe sharing (Wada et al. 1999). The incidence or prevalence of marijuana abuse among HIV patients is not known, but the overall prevalence of smoked marijuana either for anxiety and/or depression, improving appetite, or relief of pain among HIV

patients is 23 %. Among the HIV-infected IDUs, the prevalence of HCV may be as high as 90 % (Hagan and Des Jarlais 2000). In general, 15–30 % of HCV— with the following: As above, although 15-30 % of HCV-infected people clear the virus spontaneously, other individuals become chronically infected. For example, in an Irish cohort of 496 HCV-infected patients in treatment clinics, HCV viral clearance was seen in 38 % of IDUs (47 % females, 34.5 % males), was independent of age and duration of intravenous drug use, and was sustained in 82 % of the subjects for 2 years giving an overall clearance rate of 31.1 % (Keating et al. 2005). HCV genotype distribution may vary among IDUs, with 48 % with subtype 1a and 16 % with subtype 1b (Garcia et al. 1998). In Spain, the genotype 3a was prevalent in 65 % of IDUs, whereas the genotype 1b was predominant among patients who had received blood transfusions (Cilla et al. 1996).

106.2.2.2 Treatment of HCV Infection in Substance Users

During the acute phase of HCV infection, the stage of infection which is most often missed, patients may be treated successfully with a combination of peginterferon and ribavirin, the goal being to achieve undetectable RNA levels at the end of 24 weeks of treatment (Grebely et al. 2011). During the chronic phase, when the patient has displayed persistently detectable RNA and elevated ALT levels for more than 6 months with moderate inflammation, fibrosis, or necrosis on biopsy, the gold standard for staging liver disease, therapeutic regimens can consist of peginterferon alone or in combination with ribavirin as is done most frequently. Newly approved antivirals (e.g., boceprevir, telaprevir) are currently being investigated in substance-using patients with acute HCV infection but not yet among substance-using patients with chronic infection.

To complicate further the development of new antiviral agents for treating HCV infection across populations, there are at least six genotypes and more than 50 subtypes of the hepatitis C virus, each of which is likely to respond differently to therapy. For example, in the USA, approximately 70 % of the HCV patients are infected with genotype 1 and the remainder with genotypes 2, 3, and 4; however, genotype 1 has a less favorable prognosis and response to treatment than do other genotypes for currently unknown reasons. The SVR rates range between 42 % and 33 % with peginterferon and ribavirin against genotype 1, whereas the SVR rates against genotype 2 and 3 range between 79 % and 82 %. The viral load of >2 million copies/ml is not responsive to treatment with peginterferon and ribavirin. Incidentally, serious side effects of therapy such as depression and suicidal ideation remain a concern. Multiple HCV genotype infections are associated with rapid immunological and clinical progression. HIV disease progression differs by HCV genotype and is faster in individuals whose HCV infection involves more than one HCV genotype. Although it has been postulated that failure to interferon therapy in IDUs may be related to different genotypes, Soriano et al. (2005) did not find such a case among former IDUs coinfected with HIV and HCV genotypes. Other factors such as frequent injection drug use, the prevalence of other OIs, and engaging in risky

behaviors could have further negative impact on the disease progression and thus the effectiveness of treatment modality. Side effects of treatment may include fatigue, headache, fever and myalgia, bone marrow suppression with pancytopenia, hemolytic anemia, depression, suicidal ideation, and suicide. In sum, about 10–40 % of patients on interferon develop significant adverse neuropsychiatric complications serious enough to discontinue therapy. Neuropsychiatric complications are further exacerbated by injection drug use, and as such, patients on interferon alone or in combination with ribavirin should be monitored closely for serious adverse events.

106.2.3 HIV/HCV Coinfection

It has been estimated that there are an estimated ten million HIV-/HCV-coinfected persons worldwide and an estimated 250,000 people live in the USA (Thomas 2008). HIV coinfection worsens the outcome of chronic HCV infection, increasing both serum HCV RNA level and liver damage and decreasing sustained response to interferon therapy. Age and alcohol appear to be the cofactors associated with cirrhosis and mortality. Alcohol consumption in amounts greater than 50 g per day (i.e., 4–5 drinks) is also a risk factor for liver disease progression among patients with HIV/HCV coinfection. Alcohol-induced cirrhosis can result in dramatic changes in drug metabolism via compromised liver function (Kresina et al. 2002). Chronic HCV infection also accelerates the course of liver disease in HIV-infected *IDUs*, leading to cirrhosis and liver failure in a short period of time. Medical complications of chronic HCV infection may include decompensated liver disease (e.g., encephalopathy, ascites, and jaundice), gastrointestinal bleeding, hepatorenal syndrome, and peritonitis (Soriano et al. 2011). HCV-positive subjects also remain at an increased risk for death and hospitalization post-HAART even after adjustment for antiretroviral use and time-updated CD4 cell and viral load measures. Deaths and hospitalizations in HCV+ patients are primarily for non-AIDS-defining infections and complications of IDU (Klein et al. 2003). Although HIV infection accelerates the natural history of HCV infection, conversely the impact of HCV infection on the natural history of HIV infection remains unclear. It is possible that HCV infection may negatively impact on the CD4 T-cell count and thereby act as a direct cofactor for HIV disease progression. Thus, treatment of chronic hepatitis C might indirectly benefit HIV disease and should be considered in future treatment strategies (Carlos Martin et al. 2004).

Chronic HCV infection also accelerates the course of liver disease in HIV-infected IDUs, leading to cirrhosis and liver failure in a short period of time. Medical complications such as decompensated liver disease (e.g., encephalopathy, ascites, jaundice, gastrointestinal bleeding, hepatorenal syndrome, peritonitis) have been reported (Soriano et al. 2011). HCV-positive subjects also remain at an increased risk for death and hospitalization post-HAART even after adjustment for antiretroviral use and time-updated CD4 cell and viral load measures (Anderson et al. 2004).

106.2.3.1 HIV/HCV and Substance Use

Coinfection of HCV and HIV is an important and frequent scenario, especially among IDUs. The prevalence of both HIV and HCV infections ranges from 30 % to 90 %, with incidence rates between 10 % and 30 % per year. Higher levels of infections may be associated with longer duration and higher frequency of injection drug use, incarceration, and/or lack of access to needle exchange programs. Both injection-related risk factors (i.e., years of injecting drugs, type of drug injected, sharing of injection paraphernalia) and sex-related risk factors (e.g., lack of condom use, multiple sexual partners) are conducive to the spread of multiple infections such as HIV and HCV (Estrada 2002). Since both viruses share common transmission pathways, HIV-HCV coinfection prevalence may be as high as 90 % of HIV-infected IDUs in less developed regions of the world such as Central, South, and Southeast Asia and Eastern Europe (Garfein et al. 1998; Quaglio et al. 2003; MacDonald et al. 2000). In Southeast Asia, HCV prevalence has been reported to reach between 50 % and 75 % (Thomas et al. 1995), 33 % in St. Petersburg, Russia (Law 1999), and 50–55 % in Australia (Dore et al. 2003). In India, there are an estimated ten million people living with HCV infection (Abraham 2012). Between January 1992 and May 1997, the prevalence of HCV infection among 350 HIV-infected veteran patients in the USA was 33 %.

The clinical course of HIV and HCV infections may include a number of adverse health effects including rapid progression of liver disease and death (Mayor et al. 2006). The prevalence of HIV and HCV infections among mentally ill patients may also be as high as eight times that estimated for the US population (Rosenberg et al. 2001). In a large cohort of 18,349 American veterans, Backus et al. (2005) found high rates of comorbid conditions that complicated both the pharmacotherapy and clinical course of both infections. Thirty-seven percent patients were HIV positive. The HIV-/HCV-coinfected patients tended to be older men, were either African-Americans or Hispanic, reported IV drug use as a risk factor for HIV acquisition, and/or were diagnosed with depression. Some subjects described alcohol abuse, substance use, or hard drug abuse compared with HIV-mono-infected patients. The authors suggested that optimal models of integrated care should be developed for populations with HIV, HCV, and HIV/HCV coinfection and who need substance use treatment and/or mental healthcare. Neuropsychiatric consequences of dual infections among the IDUs may also include emotional stress, psychological and coping problems (obsessive compulsive, phobic anxiety, paranoid ideation, psychoticism) and less fighting spirit, and hopelessness and anxious preoccupation towards illness. Routine assessment of psychosocial variables and coping mechanisms should be integrated into all HCV and HIV services, especially those dedicated to treatment of patients with substance use, as a vulnerable segment of the population at risk for life-threatening physical illness such as HCV and HIV infections (Grassi et al. 2002). HIV-/HCV-coinfected patients are also significantly more likely to have had past opiate, cocaine, or stimulant use disorders; have significantly greater incidence rates of past substance-induced major depression; and exhibited neurocognitive impairments (e.g., diminished executive functioning) and higher rates of perseveration. HCV+ patients also frequently have higher

degree of HIV-associated dementia. Interestingly, these noted impairments in cognitive function appear to be more closely associated with serology rather than liver disease severity. Overall, the neuropsychiatric impact of HCV is significant among patients with advanced HIV/AIDS disease (Ryan et al. 2005). In a study of 185 French hospital departments involved in HIV/AIDS management, of the 822 HIV-infected patients, 29 % were infected with HCV, 8 % with HBV, and 4 % with both HCV and HBV. The most frequent causes of death among HIV-/HCV-coinfected patients were liver disease (31 %) and AIDS (29 %). The risk of death from liver disease was the highest in patients coinfected by HCV and HBV. Fifteen percent of the patients who died from liver cancer were coinfected with HBV infection (Salmon-Ceron et al. 2005).

106.2.3.2 Treatment of HIV/HCV Coinfection infection in Substance Users

There are very few treatments available for patients who have a history of substance use and are also coinfected with HIV and or HCV. Compared to HIV-infected patients, patients coinfected with HCV are less likely to be on HAART and are frequently hospitalized with higher CD4 counts for non-HIV-related medical problems including complications of liver disease (Falusi et al. 2003). On the other hand, HAART reduces the incidence of death in HIV-infected patients but with variable rates of survival due to hepatitis C viral infection and drug use. Thus, management of HCV-coinfected IDUs must be optimized to achieve a similar benefit as has been observed among other individuals on HAART (Voirin et al. 2004). Early untreated HIV infection is associated with higher HCV viremia and more severe liver injury in IDUs with chronic hepatitis C infection (Serfaty et al. 2001). However, HIV coinfection does not compromise response to interferon therapy in patients with chronic HCV infection. The rate of response between HIV+ and HIV− patients remains in the range of 36–40 %, whereas it remains at 25 % among the interferon nonresponders regardless of HIV status. In HIV+ patients, the CD4 cell count did not influence the histological response. In HIV-/HCV-coinfected patients treated with interferon, liver histological improvement is frequently similar to that observed in HIV-negative patients, thereby supporting the early treatment of chronic hepatitis C in HIV-infected patients (Di Martino et al. 2002).

On the other hand, liver transplantation (LT) is being evaluated as a safe and effective therapeutic option for HIV-infected patients with end-stage liver disease (ESLD). Longer follow-up in a larger series is needed before any conclusive directive could be provided for HCV-/HIV-coinfected patients requiring LT (Norris et al. 2004).

In substance use treatment programs such as methadone maintenance treatment (MMT), the overall HCV prevalence may be as high as 67 %, 29 % for HIV, and 26 % for HCV/HIV coinfection. The high prevalence of HCV and HIV coinfections in MMT patients varies both by current age and age at admission to MMT. The prevalence of HCV may run as high as 45 % in 35–39-year-olds, all the way up to 92 % in 45–49-year-old patients, with a linear relationship between infection

seroprevalence and age at admission into MMT programs (Piccolo et al. 2002). Collectively, these data indicate that this population would benefit greatly from risk reduction education and pharmacologic treatment for HCV and HIV.

Despite drug abusers being at high risk for HCV infection, 45–85 % may be unaware of their infection status and associated health consequences. Methadone maintenance treatment programs cover a significantly greater number of HCV-related topics and other specific topics (e.g., how to avoid transmitting HCV, the importance of testing for HCV, treatment options if HCV positive) compared to drug-free programs. However, the vast majority of drug-free programs fail to address what needs to be done if an individual is coinfected with HIV and HCV and how to maintain health if found to be HCV positive. Drug treatment programs need to (1) better educate patients much more adequately about the proactive steps an individual should take to deal with HCV, (2) provide critically needed HCV services such as screening and referral to care, and (3) encourage patients to make full use of these services (Strauss et al. 2004). However, there are programs that are about 4.5 times as likely to provide HCV education and dispense methadone to patients, almost four times as likely to provide this service if they educate most of their staff about HCV, two times as likely if they are residential, and almost two times as likely if they conduct HIV testing on-site. Collectively, this suggests there is a major need to increase HCV educational services in drug treatment programs. Walley et al. (2005) report that although one-third of opiate-dependent patients in an MMT program knew about HCV treatment, more than half became "definitely interested" in HCV treatment after hearing the risks and benefits. Whites were seven times, and Latinos were about six times more likely than African-Americans to know about HCV treatment. In general, MMT programs could play a key role in increasing access to HCV treatment and educating patients about treatment options. Education programs need to be established to disseminate: (1) patients about the dangers of substance use and co-occurring infections, (2) primary health care providers, (3) infectious disease specialists, as well as (4) hepatologists available treatment/best practices knowledge about drug addiction. Conversely, it is equally important that psychiatrists and other health care providers be trained adequately about the problems of co-occurring infections in substance users.

106.2.3.3 Treatment of IDUs Coinfected with HCV

To date, clinical management of a single infection has been relatively simple. There exist a multitude of anti-infective agents (antibiotics against bacterial infections) or antiviral agents against viral infections available in the drug armamentarium that a physician could prescribe to a patient. However, clinical management of multiple infections such as HIV, HCV, and others poses a major problem when a patient is also addicted to multiple drugs of abuse, is homeless, and possibly has other comorbid psychiatric complication and, perhaps most importantly, is not likely to adhere to a treatment protocol.

Regarding the medical management of HCV infection in IDUs, although in 1997, the NIH consensus panel (1997) recommended that IDUs should abstain

from illicit drug use for 6–12 months prior to the initiation of HCV treatment, in 2002 the NIH consensus panel recommended that individuals with active injection drug use *could be considered* for HCV treatment (Seeff and Hoofnagle 2003). These recommendations were further reinforced by the American Association for the Study of Liver Disease (AASLD) practice guidelines for diagnosis, management, and treatment of HCV (Strader et al. 2004). Accordingly, treatment of HCV infection should not be withheld from IDUs or those who are on MMT, provided they wish to take HCV treatment, and are able to maintain close monitoring and practice contraception. In addition, several investigators (Edlin et al. 2005; Sylvestre 2005; Dore and Thomas 2005) have shown that drug addicts infected with dual infections can be successfully treated. Better response to therapy is seen if patients with multiple comorbidities are treated by a multidisciplinary team in an integrated treatment facility (Taylor et al. 2005). HCV treatment is rare in the HIV-/HCV-coinfected patients, especially the nonwhite urban poor who are less likely to receive HCV testing and subspecialty referral than their white or more affluent counterparts. The US Preventive Services Task Force (USPSTF 2013; Moyer 2013) recommended screening for HCV infection in persons at high risk for infection and those born between 1945 and 1965. http://www.uspreventiveservicestaskforce.org/uspstf/uspshepc.htm. More comprehensive recommendations for the management of hepatitis C infection among people who inject drugs also have been published by Robaeys et al. (2013).

In general, drug abusers face many challenges in gaining access to health care: (1) distrust of health care system, (2) cost of therapy, (3) poor adherence to therapy, (4) physicians' prejudice, and (5) potential for reinfection from injection use. IDUs or HIV-infected patients are less likely to receive pre-therapeutic evaluation as well as appropriate antiviral therapy even after evaluation as compared to others (Cacoub et al. 2005). Adherence is important but drug use itself does not necessarily predict lack of adherence. HCV-infected IDUs can be stabilized with methadone (or buprenorphine) and treated successfully with peginterferon alone or in combination with ribavirin and adjunct drug addiction services such as psychiatric and behavioral therapy (Litwin et al. 2009).

Substance abuse treatment programs represent a vital venue for curtailing epidemics of HIV and HCV among substance-abusing populations. Currently, substance abuse treatment programs vary in corporate structure, source of revenue, patient census, and medical and non-medical staffing; medical services, counseling services, and staff education targeted HIV/AIDS more often than HCV or STIs. HCV-infected drug addicts in a treatment program can be successfully treated with methadone or naltrexone (Brown et al. 2006, 2009).

Despite expedited referrals for HCV care, only a few participants receive an evaluation, and even far fewer are treated. Because increasingly effective treatment is available, better methods must be developed to improve evaluation and treatment of HCV-infected drug users including those coinfected with HIV (Fishbein et al. 2006). Strategies to improve access to HCV treatment for current and recovering IDUs include the following: (a) drug dependency treatment; (b) education and training for hepatologists, addiction medicine physicians, and other HCV treatment

physicians; (c) development of multidisciplinary clinics; and (d) peer-based education and support for individuals considering and receiving HCV treatment (Dore and Thomas 2005). Further, treatment of HIV infection with a combination of two nucleoside analogues alone, or with an additional protease inhibitor, significantly increases CD4+ cell counts and decreases the HIV viral load with no impact on HCV viremia and ALT or AST levels (Gavazzi et al. 1998). High viral load (HCV RNA levels) is associated with a poor response to treatment of chronic HCV and vice versa; and factors such as older age, marijuana use, alcohol use, and coinfection with HIV are predictors of higher viral load among drug users.

106.2.3.4 Costs and Burden to the Society

It is difficult to estimate the global economic burden of substance use and co-occurring infectious diseases. This is because data on direct expenses associated with inpatient and outpatient health care and economic damage associated with lost productivity, etc., are needed, both of which vary within each country. As an example, the annual substance use alone cost to the US society may be as high as $559 billion (www.drugabuse.gov). Hepatitis C infection-related costs to the society in terms of treatment duration, medication costs, and medication side effects can be enormous. El Khoury et al. (2012) reported that in the USA, the cost per patient per year for of liver transplants was at $201, 110 ($178,760–$223, 460), hepatocellular carcinoma (HCC) at $23, 755–$44, 200, variceal hemorrhage at $25, 595, compensated cirrhosis at $585–$1,110, refractory ascites at $24,755, hepatic encephalopathy at $16, 430, sensitive ascites at $2,450, moderate chronic hepatitis C at $155, and mild chronic hepatitis C at $145 per year per person. In general, in the USA, the 24-week cost of treatment regimen of boceprevir is approximately $22,000; the 12-week treatment regimen cost of telaprevir is approximately $49,200. What is more, this is in *addition to* the corequisite cost of about $38,000 for peginterferon. Depending on the response to the drug, the treatment regimen is either 24 or 48 weeks. But **it must be noted that there is a pressing need to halt or slow the *current* epidemic of curable HCV infection among substance-abusing populations**. The cost of new HIV infections in the USA in 2002 was estimated at $36.4 billion, including $6.7 billion in direct medical costs and $29.7 billion in productivity losses. Direct medical costs per case were highest for whites ($180,900) and lowest for blacks ($160,400). Productivity losses per case were lowest for whites ($661,100) and highest for Hispanics ($838,000). The use of ART and more effective ART regimens decreases the overall cost of illness (Hutchinson et al. 2006).

106.2.4 Other Opportunistic Infections in Substance-Using Populations

Illicit drug use is also associated with a wide variety of bacterial infections such as tuberculosis (TB) streptococcal and staphylococcal infections (Kaushik et al. 2011).

TB is a major public health problem among IDUs, especially in HIV-infected patients. Many IDUs are uninformed about TB and their personal TB status. The threat of TB-related involuntary detainment may lead IDUs to avoid TB diagnostic procedures, TB treatment, or drug abuse treatment (Grenfell et al. 2013). Tobacco smokers of 20 years or greater duration had 2.6 times the risk of nonsmokers for TB. Opiate drug users are also at much higher risk of acquiring mycobacterial infection than the general population. Based on a survey that showed the prevalence of smear-positive pulmonary TB in opiate drug users in Iran at more than 100 times than in the general population, the investigators recommended that active screening to detect pulmonary TB should be integrated into routine testing at all harm reduction facilities for drug users, irrespective of their route of drug use or HIV status (Honarvar et al. 2013). TB represents a major public health problem in Eastern Europe. There are worsening epidemics of TB, multidrug-resistant tuberculosis (MDR-TB), and HIV in Ukraine, against a background of epidemics of STI and IDUs (Atun and Olynik 2008).

Among drug users, prevalence of various infections including STIs has been reported as HCV, 35.1 %; HBV, 29.5 %; HIV, 2.7 %; HSV-2, 44.4 %; syphilis, 3.4 %; chlamydia, 3.7 %; and gonorrhea, 1.7 %. Of the 407 subjects, 62 % had markers for one of the STDs. HIV and STIs were seen in crack cocaine-using African-Americans; HCV infection was seen in 30-year-old or older IDUs sharing needles, and HSV-2 infection was observed in 30-year-old or older African-American women (Hwang et al. 2000). The sexually transmitted infections among IDUs may include syphilis, gonorrhea, chlamydia, trichomonas vaginalis, bacterial vaginosis, herpes simplex virus (HSV) infection, and human papillomavirus (HPV) infection (Kanno and Zenilman 2002), for which excellent diagnostic tests and antibacterial or antiviral medications are available. Staphylococcus *aureus* and streptococcus species, the most common pathogens, cause the most bacterial infections among drug users. Carriage rates of *S. aureus* and methicillin-resistant S. *aureus* are higher among IDUs than they are in the general population (Atkinson et al. 2009). Drug users have a higher rate of nasal or skin colonization with *S. aureus* than among non-drug users, perhaps because their nasal epithelium has been damaged by drug inhalation, their skin has been damaged by drug injection (Gordon and Lowy 2005), and/or they do not maintain a high standard of personal hygiene. Drug users may also transmit staph or strep bacteria by sharing contaminated drug paraphernalia. Transmission drug paraphernalia and/or drug adulterants may directly affect the risk of infection with particular organisms. IDUs may develop infections of the skin and soft tissue, musculoskeletal system, endovascular system, respiratory tract, and other miscellaneous tissues/organs. The medical management of bacterial infections in drug users begins with the recognition of substance use and its associated coexisting conditions. The specific issues of the management of drug withdrawal, adherence to therapy, and difficulties of intravenous access must be a part of a comprehensive therapeutic strategy. Although conventional treatment is suggested, short courses of parenteral and oral regimens have been investigated for right-sided infective endocarditis associated with injection drug use.

106.3 Conclusion

Millions of people who abuse drugs are also coinfected with one or more infections. The consequences of both substance use and co-occurring infections are serious and can result in death if left untreated. The adverse health consequences range from immunological, neuropsychiatric, cardiovascular, and/or hepatic complications to death. An early perception among infectious disease clinicians and/or hepatologists was that substance users who presented with co-occurring infections (e.g., HIV, HCV, or other OIs) were too difficult to treat; however, research shows that substance-abusing patients enrolled in drug treatment programs (e.g., MMT) with effective and safe antiretroviral or antiviral therapies (e.g., HAART) can have very positive clinical outcome, especially if closely monitored for adherence to therapeutic regimens and managed by a multidisciplinary clinical team. In sum, there is a pressing need to halt or slow the current epidemic of co-occurring infections among IDUs on fiscal grounds alone. An improved medical management of this highly vulnerable population will have a tremendous public health benefit.

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Sleep Disorders in Addiction: An Overview

107

Michael Varenbut, Jeff Daiter, and Luke Rowsell

Contents

Abstract

The overall concept and aim of this chapter is to provide a basic sleep medicine "crash course," with a specific goal of describing a practical approach to treating the patient population afflicted with substance dependence and concomitant sleep complaints.

A sleep medicine overview will be provided, with specific emphasis on sleep physiology, nosology, and psychiatric and addictive disorders causing sleep concerns. As well, an overview of a diagnostic approach in addition to treatment

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options will be presented. The treatment of sleep disorders with both pharmacotherapy and cognitive behavioral therapy approaches will be offered.

The often-heard complaint from our patients of "Doctor, I can't sleep" is not a simple problem, but requires a simple yet comprehensive approach. The addicted population is unique and a unique "skill set" is required from clinicians treating this population.

Treatment settings vary, and the question of "who is going to do what" is important and needs to be clarified prior to approaching optimal treatment strategies. Some treatment settings include physicians from various specialties, psychologists, therapists, program workers, and other health professionals. Invoking a multidisciplinary team approach to the diagnosis and treatment of sleep disorders, and "insomnia" in particular, is crucial.

An evidence-based approach is of paramount importance as we move to superior clinical paradigms and one that should be kept in mind throughout this process.

One can utilize a "sleep assessment package" which should include intake questionnaires, sleep diaries, and other structured assessments. Avoid medications for "insomnia" whenever possible, but when pharmacotherapy is deemed necessary, this chapter offers practical guidelines and describes other available resources.

It is advisable to screen all patients for obstructive sleep apnea, first clinically, and then with sleep studies if available. And lastly, it is important to link with local sleep clinics or specialists when possible to avail yourself and your patients of a specialist opinion when needed.

107.1 Introduction

People who abuse alcohol and other substances are at high risk for sleep disturbances due to the direct effect of the substance and/or its withdrawal on their sleep architecture and their sleep-wake cycle or its effect on their behavior and daily functioning, which in turn impacts their daily need for sleep.

Sleep problems in alcoholics, for example, increase rates of relapse as evidenced by subjective and polysomnographic sleep predictors (Brower et al. 1998). Higher levels of REM predicted relapse within 3 months after hospital discharge in 80 % of patients. In other studies, those who eventually relapsed exhibited a higher proportion of REM and a lower proportion of SWS at baseline. If sleep problems lead to relapse, then treatment of those problems should improve relapse rates.

107.2 Sleep Disorders

107.2.1 Many Suffer, but Few Are Treated Properly

It is estimated that up to one third of the adult population have occasional sleep problems. Of these, one third has chronic "insomnia" as a presenting complaint. For example, between midnight and 3 a.m., it has been estimated that on any night,

two million Canadians from the total population of 35 million are awake watching television. One of every two people has taken sedatives or tranquilizers at some time, and one in five uses them frequently. Many professionals in our current society (including doctors, nurses, EMS workers, and police) work irregular sleep-wake schedules or shift work, often leading to sleep deprivation. Compared with the population at the turn of the century, we are now sleeping 1.5 h less per 24-h period. Epidemiological studies show that the EDS (excessive daytime sleepiness) in Westerners is between 5 % and 36 %. The number one cause of excessive daytime fatigue is sleep deprivation. In any given year, 20–40 % of adults complain of difficulty sleeping and 17 % consider it serious. The majority remain unrecognized and untreated. It has been estimated that the average family MD asks two questions before offering a prescription medication to deal with "insomnia." In addition, it is well known that many medical school curricula do not spend adequate time in educating young doctors in the area of sleep medicine.

107.2.2 Implications and Consequences of Sleep Problems

There are multiple very-well-publicized examples of the implications of sleep deprivation, and fatigue secondary to excessive daytime sedation has been implicated in the following world catastrophes: Exxon Valdez oil spill, Three Mile Island nuclear accident, Chernobyl nuclear plant disaster, Bhopal chemical explosion in India, and the US Space Shuttle Challenger explosion.

Sleep deprivation studies in animals have clearly shown that "sleep is necessary for survival." In 1965, a 17-year-old college student tried to set a new world record for staying awake. The resulting clinical scenario was one of frequent micro sleeps, visual and auditory hallucinations, tachycardia, hypotension, psychosis, thermoregulatory abnormalities, profound weakness, and eventual collapse at 264 h and 12 min (11 days, 12 min). Interestingly, he fully recovered after sleeping 14 h and 40 min.

Sleep-deprived people have nearly as many car accidents as drunk drivers and double the rate of car accidents as the general population. Sleep-deprived people have a higher incidence of infection and other illnesses, as sleep acts as a "host defense" against infection and facilitates the healing process.

Specific consequences of OSA (obstructive sleep apnea), one of the most common sleep disorders, include high blood pressure, cardiac arrhythmias, cerebrovascular accidents (stroke), myocardial infarction, erectile dysfunction, and fatalities from driving while fatigued. Psychological manifestations of sleep apnea include depression and anxiety.

Sleep disorders medicine, from a historical and international perspective, is a relatively new field and one which many countries have little access to. The field largely began at Stanford University in 1970 and, as an example, is only approximately 25 years old in Canada. In 1981 with the introduction of CPAP (continuous positive airway pressure – used to treat obstructive sleep apnea), the field grew exponentially. There are currently available fellowship programs and board certification via the American Board of Sleep Medicine.

107.2.3 Sleep Laboratory and Sleep Disorders Centers

Most sleep laboratories deal with respiratory sleep disorders, such as obstructive sleep apnea (OSA), with a significant few providing the full range of sleep disorders diagnosis and treatment. The goal is to produce a technically pure polysomnogram (PSG or "sleep study"), which is the mainstay of sleep diagnostics and akin to the ECG for a cardiologist. Sleep specialists' backgrounds also differ widely and range from those whose primary training is, for example, in respirology, neurology, and psychiatry, and some who are board certified in sleep disorders medicine as well.

The PSG (polysomnogram, sleep study) is complex and labor intensive, often generating volumes of information which would be equal to 1,000 pages of data. A typical overnight sleep study monitors EEG (electroencephalogram), EOG (electroocculogram), chin EMG, EKG, respiratory effort (chest and abdominal movements), oxygen saturation, and leg movements (EMG), all using noninvasive leads. Some centers also perform MSLTs (multiple sleep latency tests) for narcolepsy and MWT (maintenance of wakefulness tests) for excessive daytime sedation differentiation.

107.2.4 Sleep Physiology

107.2.4.1 Normal Human Sleep

The exact function of sleep is still not precisely known. There is no "normal" amount of sleep that an individual needs, but the amount that one person needs is typically constant. It is estimated that 20 % of the population sleeps less than 6 h (short sleepers) and 10 % sleeps 9 h or more (long sleepers).

Sleep produces different EEG signals that range from wake patterns of beta waves to relaxed states with eyes closed producing alpha waves. Deeper sleep produces slower and bigger theta and delta waves.

There are two broad types of sleep: REM (rapid eye movement) and NREM (non-REM).

107.2.4.2 Normal NREM Sleep

NREM sleep is divided into three stages: stage N1 with low-amplitude mixed-frequency waves (predominantly in the 4–7Hz theta frequency) and slow rolling eye movements, stage N2 typified by theta frequency waves and the presence of physiological features known as "sleep spindles" and "K-complexes," and stage N3 featuring the emergence of slow (0.5–2 Hz) delta frequency waves.

107.2.4.3 Normal REM Sleep

Even without any instruments, we can tell if someone is in REM sleep by looking at the movements in their eyes, even when closed. In REM, we are usually dreaming, but not always. Alpha motor neuron activity is suppressed through a number of inhibitory pathways, and our skeletal muscles are typically paralyzed. REM periods typically occur every 90 min, with each successive REM phase getting longer in

duration: 1st, 5 min; 2nd, 10 min; and 3rd, 15 min. Blood flow is directed to the brain (active), and the EEG pattern is that of low-amplitude, mixed-frequency waves, often with the presence of distinct waves with a sawtooth appearance.

REM deprivation is associated with anxiety and agitation, and our primary drives (eating) are less controlled. In addition, most dreams are forgotten, unless we wake from them.

Historically, it was thought that sleep was simply the absence of wakefulness, resembling death. It is now well known that this is not the case, and on the contrary, sleep is an active process.

Sleep is not a homogeneous state, but rather a combination of two separate and distinct states: non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. This characterization is based on behavioral and physiologic changes that occur during these phases of sleep. NREM sleep accounts for 75–80 % in adult humans and is further divided into three stages, based on EEG criteria.

- Stage N1 Sleep → 3–8 % of total sleep time
- Stage N2 Sleep → 45–55 %
- Stage N3 Sleep → 15–20 %

Sleep normally cycles through the various stages as follows: generally stage N1 → stage N2 → stage N3 → stage N2 → REM → stage N1, N2, or N3. A full sleep cycle consists of a sequence of NREM and REM sleep, typically lasting approximately 90–110 min, and there are generally 4–6 cycles per night. The first two cycles are dominated by SWS (slow-wave sleep), and REM sleep increases as the night progresses.

Sleep patterns also change throughout our lifespan, with sleep occupying two thirds of a human newborn's time and REM sleep occupying one half of total sleep time. The percentage of REM declines rapidly in early childhood, and by the age of 10, the adult percentage of REM sleep is achieved. SWS is minimally present in the newborn but rapidly increases to reach maximum by the age of 10 and then declines.

107.2.5 Classification of Sleep Disorders

107.2.5.1 International Classification of Sleep Disorders

The **International Classification of Sleep Disorders** (ICSD) is "a primary diagnostic, epidemiological and coding resource for clinicians and researchers in the field of sleep and sleep medicine" (American Academy of Sleep Medicine 2005).

The ICSD is produced by the American Academy of Sleep Medicine, in association with the European Sleep Research Society, the Japanese Society of Sleep Research, and the Latin American Sleep Society. The ICSD was first published in 1990. In 1997 it was revised; the title was changed to *The International Classification of Sleep Disorders, Revised* (*ICSD-R*), and the authorship was changed from "Diagnostic Classification Steering Committee, Thorpy MJ, Chairman" to "American Academy of Sleep Medicine". A second edition, called ICSD-2, was published in 2005.

The ICSD-2 was published with the goal of standardizing definitions of sleep disorders and creating a systematic approach to diagnosis. It is widely used by

clinicians and researchers worldwide, improving research efforts throughout the international community by adhering to a recognized set of standards. The ICSD-2 outlines the following goals:

1. To describe all currently recognized sleep and arousal disorders and to base the description on scientific and clinical evidence
2. To present the sleep and arousal disorders in an overall structure that is rational and scientifically valid
3. To render the sleep and arousal disorders as compatible with ICD-9 and ICD-10 as possible

As a result, the ICSD-2 organizes sleep disorders into the following eight categories:

1. Insomnias
2. Sleep-related breathing disorders
3. Hypersomnias of central origin not due to a circadian rhythm sleep disorder, a sleep-related breathing disorder, or other causes of disturbed nocturnal sleep
4. Circadian rhythm sleep disorders
5. Parasomnias
6. Sleep-related movement disorders
7. Isolated symptoms, apparent normal variants, and unresolved issues
8. Other sleep disorders

107.2.5.2 Psychiatric Disorders and Sleep

Troubled minds have troubled sleep – Shakespeare

Almost all mental disorders can have an associated sleep disturbance. Insomnia often sets the stage and is a major risk factor in the development of a psychiatric disorder. If we can treat insomnia, it may protect against significant mental illness.

The brief overview of the selected disorders below has also been found to be very commonly associated with substance use disorders of all types. Being aware of the specific sleep parameters and common presentations of these conditions can assist tremendously in the overall approach to sleep disorders in the substance use population.

The ICSD lists psychoses, mood disorders, anxiety disorders, panic disorders, and alcoholism.

The following section will aim to provide a brief description of the most commonly seen sleep architecture problems seen in the major mental disorders.

Sleep architecture and parameters characteristic of schizophrenia-associated sleep disorders: Sleep continuity disturbance, reduced SWS (slow-wave sleep/deep sleep), decreased REM latency (time to first REM episode), increased REM sleep (total percent of REM), and REM sleep "hallucinatory activity".

Sleep architecture changes typical of depression: Long sleep latency (from time to bed, to first sleep episode), shortened REM sleep latency (time to first REM episode), increased REM density, reduced TST (total sleep time), reduced sleep efficiency (total sleep time, divided by time in bed), increased awakenings, decreased SWS (slow-wave sleep, deep sleep).

It has been estimated that 90 % of cases of major depression have associated symptoms of insomnia. Sleep architecture and parameters can also be used to enhance pharmacotherapy. For example, clinical response to antidepressant medications is improved if the following can be achieved: persistent prolongation of REM latency, persistent reduction of total REM sleep time, and persistent reduction in REM density.

107.2.5.3 Sleep Consequences Associated with Anxiety Disorders

GAD (**Generalized Anxiety Disorder**): Prolonged sleep-onset latency, increased stages 1 and 2 sleep, less SWS (slow-wave/deep sleep), decreased REM sleep percentage, and increased or normal REM latency.

Approximately 70 % with panic disorder have initiation and or maintenance insomnia. Nocturnal panic is most common in NREM sleep and just before the onset of SWS. Nocturnal panic occurs in ~70 % of those with panic disorder. Nocturnal panic attacks result in worse daytime panic attacks and more somatic symptoms.

OCD (**Obsessive Compulsive Disorder**) **Sleep Characteristics**: Decreased total sleep time, increased number of awakenings, shortened REM sleep latency, reduced sleep efficiency, and reduced stage 4 sleep.

PTSD (**Post-traumatic Stress Disorder**) **Sleep Characteristics**: Frequent nightmares are a "hallmark," increased WASO (wake after sleep onset), increased sleep-onset latency, reduced SE (sleep efficiency), and increase in RBD (REM behavior disorder).

Personality Disorders: Personality disorders have been commonly associated with insomnia symptoms. These disorders are lifelong personality traits, which can be categorized as eccentric, schizotypal forms of behavior or erratic, labile, and aggressive characteristics typical of narcissistic or borderline personality disorders.

Patients with borderline personality disorder have been found to have a sleep architecture remarkably similar to those with major depression.

107.2.5.4 Comorbid Conditions and Disorders Causing Sleep Concerns

It is well recognized that primary sleep disorders, psychiatric conditions, substance use disorders, and psychiatric medications can all affect sleep quality and architecture. There are also many primary medical disorders and conditions which can cause sleep difficulties. These would include a myriad of neurologic, cardiovascular, pulmonary, gastrointestinal, genitourinary, endocrine, musculoskeletal, and reproductive conditions.

107.2.6 Contributing Medications and Substances Causing Sleep Problems

The majority of people with substance abuse or dependence experience some form of sleep disorder. While the effects of alcohol have been most studied, there is sufficient evidence on the direct effect on sleep architecture and parameters by a great variety of substances (see Table 107.1 below).

Table 107.1 Common medications and substances contributing to sleep concerns

Category	
Antidepressants	SSRI (fluoxetine, paroxetine, sertraline, citalopram, escitalopram, fluvoxamine), venlafaxine, duloxetine, MAO inhibitors
Stimulants	Caffeine, methylphenidate, amphetamine derivatives, ephedrine and derivatives, cocaine
Decongestants	Pseudoephedrine, phenylephrine, phenylpropanolamine
Narcotic analgesics	Oxycodone, codeine, morphine, propoxyphene, methadone
Cardiovascular	Beta-blockers, alpha agonists and antagonists, diuretics, lipid-lowering agents
Pulmonary	Theophylline, albuterol

107.2.6.1 Stimulants

Nicotine, caffeine, amphetamines, and cocaine can all cause increased arousal acutely and then subsequently cause hypersomnia and fatigue or sedation upon withdrawal.

Cocaine has been shown to increase awakenings and cause poor sleep quality by directly affecting dopamine levels.

107.2.6.2 CNS Depressants

Benzodiazepines, alcohol, and opioids can all cause excessive sedation and fatigue acutely while causing insomnia upon withdrawal. The effects of prescribed benzodiazepines for other indications, such as anxiety, require close monitoring and caution in patients with a history of substance dependence (Ciraulo and Nace 2000).

Heroin causes a decrease in stage 3 and 4 sleep and a decrease in REM sleep with frequent awakenings. Heroin withdrawal typically has been shown to cause REM rebound effect and more frequent nightmares.

107.2.6.3 Alcohol

Acute effects of alcohol intake include increased sleepiness approximately 30 min after ingestion, decrease in awakenings for the first 4 h but increase for the last 3 h, and an increase in dreams (often anxious dreams) (Aldrich 1998).

Chronic effects of alcohol use include increased sleep fragmentation and shorter SWS (slow-wave sleep) interrupted by brief arousals, and an increase in alcohol intake improves the above symptoms, which typically leads to a worsening problem (Landolt et al. 1996).

107.2.6.4 Alcohol Abuse and Dependence

Insomnia is a common feature for alcoholism with prevalence rates of 36–72 %. Alcohol is an REM suppressant but improves slow-wave sleep in the first half of the night.

The initial effect is relaxation and sedation but it also causes increased "WASO" (wake after sleep onset) and increased fragmentation during the second half of the night. Withdrawal from alcohol causes an increase in REM (nightmares), increased

WASO, and decrease in stage 3 or 4 sleep. Insomnia may also be a risk factor for relapse (Brower 2001, Brower et al. 2003).

107.2.7 Diagnosis of Sleep Disorders

The goal of this section is to provide a brief overview of a diagnostic approach to diagnosis of a variety of sleep disorders, with specific emphasis to substance use disorder patients. This section will cover initial sleep intake history and physical examination, sleep diary or log, and sleep questionnaires.

107.2.7.1 Intake History and Physical Examination

Much like with any other medical conditions, it is of paramount importance to obtain a full medical and psychiatric history. Specific to sleep disorders, it is important to include a bed partner or caregiver interview. Discussion about the patient's sleep habits and daytime functioning should be undertaken. Specific and detailed analysis of substance use or abuse is crucial. This should include both licit (e.g., tobacco, caffeine, alcohol) and illicit substances, as these can all have an effect on sleep.

The physical examination should be targeted at ruling out specific diagnosis but should typically include a mental status examination (e.g., mini mental status), as well as a cardiovascular, respiratory, and neurologic examination.

Specific details on a "typical" night's sleep should be obtained and should include the following:

- Time to bed
- Delay to onset of sleep
- Specific symptoms or behaviors delaying sleep onset
- Awakenings – number, duration, and cause if known
- Time of final awakening
- Time out of bed
- Total estimated duration of sleep (TST – total sleep time)
- Nocturnal behaviors – e.g., eating, smoking, and nocturia
- Napping behavior during daytime

The details above can be tabulated in detailed notes or by the use of a sleep "diary" or "log."

A variety of standardized sleep questionnaires exist that can be used to provide an objective characterization of specific sleep parameters, depending on the clinical situation at hand. The table below includes the most commonly used questionnaires and a brief description of same (Table 107.2).

107.2.7.2 Sleep Questionnaires

The Epworth Sleepiness Scale is a widely used and accepted questionnaire that a patient can complete in a few minutes and can help assess the patient's subjective level of sleepiness (excessive daytime sedation). This is of particular importance to assess daytime effects of sleep disorders. The scale is copyright protected but is

Table 107.2 Examples of insomnia questionnaires used in baseline and treatment outcome assessment

Questionnaire	Description
Epworth sleepiness scale	ESS is an 8-item self-report questionnaire used to assess subjective sleepiness (score range: 0–24; normal <10)
Insomnia severity index	ISI is a 7-item rating used to assess the patient's perception of insomnia
Pittsburgh sleep quality index	PSQI is a 24-item self-report measure of sleep quality (poor sleep: global score >5)
Beck depression inventory	BDI (or BDI-II) is a 21-item self-report inventory used to measure depression (minimal or no depression: BDI <10; moderate to severe: BDI >18)
State-trait anxiety inventory-form Y trait scale	STAI is a 20-item self-report inventory used to measure anxiety (score range: 20–80; minimum anxiety: T score <50; significant anxiety: T score >70)
Fatigue severity scale	FSS is a 9-item patient rating of daytime fatigue
Short form health survey (SF-36)	SF-36 is a 36-item self-report inventory that generically measures quality of life for any disorder (range from 0 (poorest) to 100 (well-being))
Dysfunctional beliefs and attitudes about sleep questionnaire	DBAS is a self-rating of 28 statements that is used to assess negative cognitions about sleep

available for private clinical use free of charge and can be accessed at the following web address: http://epworthsleepinessscale.com.

107.2.8 Treatment of "Insomnia"

The aim of this section is to provide a brief overview to an approach to deal with insomnia complaints in the substance use population. This is by no means an exhaustive account of each technique used, but rather a "primer" to introduce each modality.

The overall approach is that of identifying and treating the underlying condition, as well as perpetuating factors. One can then utilize a combination of behavioral, psychological, and pharmacological modalities, depending on the specific clinical presentation and patient needs.

Predisposing factors to insomnia typically include varying tendencies toward psychological, emotional, or cognitive arousal that promotes insomnia but insufficient to cause insomnia without the presence of other factors.

Precipitating factors are often identifiable events that initiate insomnia and can be major (e.g., bereavement) or minor (e.g., sleeping in unfamiliar bed). These also often depend on the predisposing arousal level of the individual.

Perpetuating factors include poor sleep habits that develop during episodes of insomnia such as erratic sleep-wake schedules, nocturnal eating, and excessive worry about sleep.

Table 107.3 Sleep hygiene rules: the dos and don'ts of a good night's sleep

1. Keep a regular schedule. Go to sleep and wake up roughly at the same time each day, even on the weekends
2. Exercise regularly, in the morning or afternoon. Don't exercise in the late evening
3. Have a comfortable bed in a quiet, dark room. Don't have your bedroom too hot or too cold
4. If hungry before bed, eat a light snack or have a glass of milk. Don't eat a heavy meal before retiring
5. Schedule a relaxing period before retiring
6. Keep the bedroom just for sleeping, sickness, and sex (3-S's), not as an all-purpose activity area
7. Don't use alcoholic beverages or recreational drugs as sedatives
8. Don't try too hard to fall asleep. Get out of bed and return to bed only when you feel sleepy (30 min rule)
9. Don't nap during the day
10. Don't smoke or drink caffeinated beverages or eat foods for several hours before bedtime
11. Use an alarm clock to wake you at your regular time, but position it away from you so you don't "clock watch" which can cause unnecessary tension
12. If worrying keeps you awake, set aside a 15-min "worry" period to occur at the same time, perhaps after dinner, and in the same place every day. Writing down a "problem" list may help to relieve stress associated with worrying about forgetting certain things

107.2.8.1 Treatment of Chronic Insomnia: An Overview

The overall approach is to identify and treat underlying condition(s) and to identify and treat perpetuating factor(s). This is best achieved with a combined approach which includes behavioral, psychological, and pharmacological strategies.

107.2.8.2 Sleep Hygiene Therapy

Sleep hygiene therapy typically makes an attempt to educate the patient about healthy sleep habits, exercise, caffeine consumption, eating behaviors, and sleep environment.

These suggestions may be ineffective alone in yielding results; they are usually a part of most behavioral treatments for insomnia. Above is an example of a list of sleep hygiene "rules" that can be utilized for this approach (Table 107.3).

You may choose to focus on two or three of the above recommendations at a time and reevaluate your sleep habits every few weeks. And remember, a consistent sleep schedule works best.

107.2.8.3 Behavioral Therapy

Behavioral therapies for insomnia that are empirically supported include stimulus control, progressive muscle relaxation, and paradoxical intention, with sleep restriction, biofeedback, and multifaceted cognitive behavioral therapy, also probably efficacious treatments (Benca 2005).

107.2.8.4 Stimulus Control Therapy

Based on the theory that cues in the bedroom precipitate and perpetuate arousal. The therapy involves instructions such as the following: "Go to bed only when sleepy," "Establish standard wake up time," "Avoid using the bedroom as

an all-purpose activity area, restricting behaviors to the 3 S's (sleep, sickness, sex)," and "Refrain from napping during the day."

107.2.8.5 Sleep Restriction Therapy

The therapy restricts time allotted for sleep each night. First, a "sleep log or diary" is maintained for 2 weeks and then initial TIB (time in bed) prescription is set at a minimum of 5 h of total bed time. This is followed by an expansion of a 15–30-min sleep at the end of the sleep phase (i.e., desired wake time), every few days. This is carried out over a few visits, with fine-tuning as needed.

107.2.8.6 Progressive Muscle Relaxation

Based on the theory that mental relaxation will be a natural outcome of physical relaxation, leading to sleep.

The patient is instructed to tense or tighten one muscle group, then release tension; muscle groups are tightened and relaxed one at a time in a specific order. A greater degree of muscle tension is attempted subsequently as familiarity increases.

107.2.8.7 Paradoxical Intention

Performance anxiety contributes to preventing proper sleep. The patient is encouraged to stay awake (the feared behavior). As the patient stops trying to fall asleep, the performance anxiety related to attempting to fall asleep is reduced.

107.2.8.8 Biofeedback

Teaches patients to facilitate increased slow brain wave activity (and thus facilitate falling asleep) by using electroencephalographic (EEG) monitoring of brain waves. Eventually this skill can be applied without the EEG.

107.2.8.9 Multifaceted Cognitive Behavioral Therapy

The goal is to identify dysfunctional beliefs and attitudes about sleep and replace them with more adaptive substitutes.

The treatment targets the following: Unrealistic sleep expectations ("I must get eight hours of sleep per night"), misconceptions regarding causes of insomnia ("My insomnia is due to a chemical imbalance"), amplification of consequences of insomnia ("I can do nothing after a bad night's sleep"), and performance anxiety due to excessive attempts at controlling the sleep process.

This is also referred to as CBT-I (cognitive behavioral therapy for insomnia) and involves a combination of cognitive and behavioral modalities.

Topics commonly addressed are an array of cognitive, circadian, and sleep-inhibitory factors that affect primary insomnia.

The combination of SCT (stimulus control therapy) and SRT (sleep restriction therapy) has proven most efficacious (Smith et al. 2002).

Cognitive behavioral therapy enhances sleep-related self-efficacy and reduces depressive and anxiety symptoms. It has also been shown to correct dysfunctional

beliefs about sleep and to reduce the use of sleep medications, with an overall improvement in insomnia-related sleep-wake symptoms.

CBT-I should be the standard treatment regimen for all insomnia patients, as comparative data suggest that CBT-I is associated with a greater and more durable benefit than pharmacologic therapy and may have an indirect effect of preventing drug dependence and relapse (Kupfer and Reynolds 1997).

107.2.9 Pharmacotherapy of Insomnia in the "Addiction Population"

107.2.9.1 Introduction

People who abuse alcohol and other substances are at a high risk for sleep disturbances due to the direct effect of the substance or its withdrawal on their sleep architecture and their sleep-wake cycle. The drug effect on their behavior and daily functioning, which in turn impacts their daily need for sleep, is also paramount (Eder 2002).

Benzodiazepines are the most commonly used prescription medication with good evidence of their effectiveness both objectively and subjectively. However, in those with a history of substance abuse, the potential for abuse of these substances is likely. In this population, alternative indicated medications such as melatonin receptor agonists (for sleep-onset insomnia) and histamine-1 antagonists (for sleep maintenance insomnia) may be preferential due to their low risk of abuse. Over-the-counter medications and off-label uses of antidepressant medications may also be considered, although limited evidence on efficacy, dosage, and safety is of concern.

107.2.9.2 OTC (Over-the-Counter) Preparations

The most commonly used medications in this class are diphenhydramine and dimenhydrinate.

107.2.9.3 Diphenhydramine

Some of the more commonly available brand names are sold as Excedrine® PM, Benadryl®, Tylenol® Allergy Sinus, Tylenol® Flu Nighttime Max Strength Powder, and Tylenol® PM.

This drug works as an antihistaminic agent, to decrease sleep latency (sleep onset), and also disrupts sleep architecture by decreasing REM sleep and increasing slow-wave sleep. The anticholinergic effect in the morning leads to drowsiness, especially in higher doses (Marzanatti et al. 1989). The potential for diphenhydramine-related toxicity and drug-drug interactions is substantial (Lessard et al. 2001), and tolerance to its sleep-inducing effects occurs within a few days (Richardson et al. 2002), suggesting that diphenhydramine and related compounds such as dimenhydrinate should not represent a viable treatment strategy for long-term sleep maintenance in chronic insomnia.

Table 107.4 Drugs with an FDA indication for insomnia

Generic name	Trade name	Dose (mg)	Mechanism of action	T max(h)	T ½ (h)
Flurazepam	Dalmane	15, 30	BzRA	0.5–1.0	47–100
Triazolam	Halcion	0.125, 0.25	BzRA	2	1.5–5.5
Temazepam	Restoril	7.5, 15, 30	BzRA	1.2–1.6	3.5–18.4
Estazolam	ProSom	1, 2	BzRA	0.5–6	Oct-24
Quazepam	Doral	7.5, 30	BzRA	2	39–73[a]
Zolpidem	Ambien	5, 10	BzRA	1.6	1.4–4.5
Zaleplon	Sonata	5, 10, 20	BzRA	1	1
Eszopiclone	Lunesta	1, 2, 3	BzRA	1	6
Zolpidem CR	Ambien CR	6.25, 12.5	BzRA	1.5	2.8
Zolpidem (sublingual)	Intermezzo	1.75, 3.5	BzRA	0.5–0.75	1.4–3.6
Ramelteon	Rozerem	8	MtRA	0.75	1.0–2.6
Doxepin	Silenor	3, 6	H1Ant	3.5	15.3–31[b]

BzRA benzodiazepine receptor agonist, *FDA* Food and Drug Administration, *H1Ant* histamine 1 receptor antagonist, *MtRA* melatonin receptor agonist
[a]Half-life for active metabolites
[b]Half-life for parent drug and active metabolite

107.2.9.4 Valerian

This older compound had been used for many years, in a variety of preparations and forms depending on country of origin. While there is some subjective improvement in the quality of sleep, there is little scientific evidence documented in clinical trials (Hadley and Petry 2003).

107.2.9.5 Prescription Medications

Benzodiazepine Receptor Agonists

These are the most commonly prescribed class of medications used for sleep. They are nonselective GABA-ergic (similar to Etoh) with effects on w1 receptors (causing sedation) and w2 receptors (with effects on memory and concentration). Commonly available and prescribed medications are zolpidem (Ambien), zaleplon (Sonata), zopiclone (Imovane), and eszopiclone (Lunesta). Eszopiclone (Lunesta) is the only hypnotic that is FDA approved without a specified time limit on the duration of prescription (Table 107.4).

The hypnotic efficacy of BzRAs has been well documented using objective and subjective measures of sleep induction, maintenance, and duration in clinical trials, as well as in meta-analyses (Holbrook et al. 2000). Thus, it can be concluded that they are effective.

Adverse reactions to BzRA hypnotics include residual effects, which can be related to the half-life of the specific hypnotic, falls in the elderly, amnesia, rebound insomnia, amnesic parasomnia episodes, and potential for abuse.

Behavioral dependence has been noted in daily and long-term use of anxiolytic BzRAs, as opposed to short-term (8/24 h) use as with hypnotics. Short-term studies (<2 weeks) (Roehrs et al. 1996) and a long-term study (12 months) (Roehrs et al. 2011) of hypnotic BzRA use did not indicate dose escalation.

However, the FDA has designated BzRA hypnotics as controlled substances, giving them a schedule IV designation, which indicates these drugs have a known abuse liability, and this must be a particular concern when prescribing these hypnotics to a patient with a history of substance abuse.

107.2.9.6 Melatonin Receptor Agonist (Ramelteon)

Ramelteon has an FDA indication for sleep-onset insomnia, supported by subjective and objective studies showing that sleep onset is hastened along in a dosage range of 4–32 mg (Erman et al. 2006; DeMicco 2006).

Adverse events report included somnolence, fatigue, dizziness, and nausea, all occurring at rates <5 %, and based on behavioral assessments of abuse liability, no liability was seen (Griffiths 2005).

107.2.9.7 Histamine-1 Antagonist (Low-Dose Doxepin)

Doxepin is a tricyclic antidepressant that is frequently used off-label as a hypnotic in antidepressant doses (25–150 mg). At the doses approved for insomnia (3–6 mg), doxepin is thought to be a relatively pure H1 histaminic receptor antagonist, which, when antagonized, produces sedating effects, without anticholinergic, antiserotonergic, and antiadrenergic activity. Doxepin has been shown in both adults and the elderly to maintain sleep, particularly in the last 2 h of the night, unlike the BzRAs, without producing residual effects. Doxepin is not a scheduled drug and is considered not to have an abuse liability; however, more evidence on this is required due to behavioral dependence of H1 antihistamines. As the clinical trials have all been short and intermediate term (≤3 months), the issue of dependence must be more fully studied before caution of low-dose doxepin is raised.

107.2.9.8 Other Off-Label Drugs Used to Treat Insomnia

Antidepressants

The most commonly used off-label drugs for insomnia are antidepressants used at "lower doses" for insomnia than their standard antidepressant doses (Walsh 2004). Trazodone, amitriptyline, and mirtazapine are three of the most widely used antidepressants. There is limited information regarding the dose range along which these drugs improve sleep and their safety at those doses. No studies of amitriptyline and mirtazapine on primary insomnia were found in literature, and two studies of trazodone gave mixed results with improvements at lower doses giving reduced sleep latency and increased total sleep time; however, these effects lasted for only 1 week.

The dosage generally recommended for sedation is lower than the antidepressant dosage, and it is not known where potential serious side effects documented at

higher doses – suicidality, residual effects, anticholinergic effects (i.e., dry mouth, urinary retention, and hallucinations) to orthostatic hypotension, priapism, cardiac arrhythmias, and conduction abnormalities – would occur at these low doses. Given that there is no clear understanding in regard to the dose range for the hypnotic efficacy and safety of these drugs, it is recommended they not be used as hypnotics.

There is currently no data available on antidepressants for use in sleep disorders among patients with substance use disorders.

Proper diagnosis of comorbid mood disorder may indicate that a single medication can be helpful to treat both conditions.

Atypical Antipsychotics

This class of medication includes "off-label use" of such drugs as olanzapine (Zyprexa) and quetiapine (Seroquel) for their effect on sleep parameters.

These agents have shown improvement in self-reported sleep measures (Roehrs and Roth 2012); however, the concern for the use of these drugs, as with the other off-label drugs, is that there is limited information regarding efficacious and safe doses, and their use as hypnotics is not recommended (National Institutes of Health 2005). There is currently no data available on olanzapine or quetiapine among patients with substance use disorders.

Off-Label BzRAs

Anxiolytic BzRAs are also often used as hypnotics, with clonazepam, alprazolam, and lorazepam the most commonly used off-label BzRAs. These share the same hypnotic mechanism of action of the indicated BzRAs and were used previously due to no limitations on long-term use; however, their hypnotic dose is unknown, and due to the above, there is no advantage to their use.

Guidelines for Prescribing Sedative/Hypnotics

- Initiate hypnotic use with identifying and addressing specific behaviors, circumstances, and underlying disorders contributing to insomnia
- Prescribe the lowest effective dose of the hypnotic
- Avoid hypnotic use or exercise caution if the patient has a history of substance abuse, myasthenia gravis, respiratory impairment, or acute cerebrovascular accident
- Prescribe hypnotics for short durations (2–4 weeks) and intermittently (duration based on the patient's return to an acceptable sleep cycle)
- Watch for requests for escalating doses or resistance to tapering or discontinuing hypnotic
- Hypnotics should be discontinued gradually (i.e., tapered); the physician should be alert for adverse effects (especially rebound insomnia) and withdrawal phenomena

General Comments About Sedatives/Hypnotics

- Administration on an empty stomach is advised to maximize effectiveness
- Not recommended during pregnancy or when nursing
- Caution is advised if signs/symptoms of depression, compromised respiratory function (e.g., asthma, COPD, sleep apnea), or hepatic heart failure are present
- Caution and downward dosage adjustment is advised in the elderly
- Safety/effectiveness in patients <18 years not established
- Additive effect on psychomotor performance with concomitant CNS depressants and/or alcohol use
- Rapid dose decrease or abrupt discontinuance of benzodiazepines can produce withdrawal symptoms, including rebound insomnia, similar to that of barbiturates and alcohol

Certain antidepressants (amitriptyline, doxepin, mirtazapine, paroxetine, trazodone) are employed in lower than antidepressant therapeutic dosages for the treatment of insomnia. These medications are not FDA approved for insomnia and their efficacy for this indication is not well established

107.2.9.9 Medications and Potential for Abuse

Abuse Liability Signs

There is abuse liability associated with the BzRA hypnotics. The non-BzRAs that are not scheduled have limitations in regard to their indications, ramelteon being only for sleep-onset and doxepin only for sleep maintenance insomnia. Therefore, a BzRA may be prescribed. The following important signs have been identified of physical/behavioral dependence on BzRAs (Kan et al. 2004):

1. Dose escalation beyond the indicated clinical hypnotic dose within the first week of treatment.
2. Use during daytime with multiple daytime doses being taken.

These patterns suggest nonhypnotic drug effects that were being sought and guidance to closely monitor the patient during the first week of use, and not allowing patient-initiated dose adjustments is recommended.

Precautions and Contraindications

Patients who have histories of drug or alcohol abuse with difficulty sleeping, particularly sleep maintenance, which is a chief complaint among abstinent alcohol and drug abuse patients, require precautions; these disturbances can continue for a year or more. The non-BzRA, low-dose doxepin may be an option, though further studies may uncover suspected dependence potential. If the physician considers the use of a BzRA hypnotic in an outpatient setting, the patient must be monitored closely beyond the initial week of use. Within the alcohol and drug abuse treatment community, stress-induced relapse is a well-recognized phenomenon that can occur

after months of successful abstinence. In such cases, the experience of new life stresses can induce a relapse to drug and alcohol abuse.

107.3 Conclusion

Insomnia is a prevalent symptom in those with chemical dependency, and it may be a predictor of relapse. The key is proper assessment and diagnosis of the underlying cause. Treatment with pharmacotherapy and behavioral therapy is likely the best option. As of this writing, there is still significant need for further research.

It is crucial to remember that not all "insomnias" are the same. The complaint of insomnia is extremely common, with significant implications and with a high rate for concurrent disorders: medical, psychiatric, and addiction. There is a need for a simple yet comprehensive approach for the diagnosis and treatment of sleep disorders in the substance-abusing population, which should involve a multidisciplinary team approach to care.

Sleep disorders medicine is a fascinating and rapidly growing field. Think about sleep disorders when patients complain of fatigue or EDS (excessive daytime sedation). Think about the possibility of OSA (obstructive sleep apnea) if the patient presents with snoring with fatigue, and they are also overweight or have hypertension or diabetes. It is prudent to stay away from benzodiazepines for insomnia as the first attempt at "treatment."

It is important to think of the ICSD classification system (as discussed earlier) and a differential diagnosis of the sleep complaint. "Insomnia" is not a diagnosis, but rather a presenting symptom.

The use of a sleep diary or log for a clear objective picture is very helpful clinically, and CBT-I accompanied by sleep hygiene modifications is the first-line "treatment" for most patients.

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Endocrine Manifestations of Addictive Diseases

108

Richard Hallinan

Contents

Abstract

Endocrine manifestations of addictive diseases range from overt clinical syndromes, such as alcoholic Cushingoid syndrome, alcoholic hypoglycemia or ketoacidosis, and opioid-related hypogonadism, to subclinical disturbances, such as blunted adrenal or thyroid stress responsiveness. They include acute and chronic toxicological processes (such as alcoholic cirrhosis or pancreatitis) or predictable side effects (such as opioid-associated hypogonadism) that are incidental to the addiction process but also disturbances of endocrine and neuroendocrine function that are intrinsic to the pathophysiology of addiction.

Increasing evidence points to effects of prenatal drug exposure and early life stress in disturbed hypothalamic-pituitary-adrenal axis regulation later in life, of

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sexually dimorphism in responses to addictive substances, and of involvement of sex hormones, oxytocin, and appetitive hormones to modulate the effects of drugs in humans.

In the addiction medicine settings, hypo- and hyperthyroidism are standard differential diagnoses for mood or anxiety disorders. Hypogonadism and/or hyperprolactinemia may cause sexual dysfunction, infertility, or gynecomastia. Psychoactive substances can contribute directly or indirectly to disturbances of glucose metabolism. Comprehensive assessment and management of people with substance use disorders may require attention to issues of metabolic and bone health.

The aim of this chapter is to foster the recognition and appropriate management of clinically important endocrine disturbances when they occur, also the appreciation of subtle endocrine and neuroendocrine effects contributing to withdrawal, craving, and relapse, better to inform counseling of patients, the understanding of laboratory tests, and making the reader aware of potential therapies arising out of the increasing body of knowledge in this area.

108.1 Introduction

Endocrine manifestations of addictive diseases range from overt *clinical* syndromes, such as alcoholic Cushingoid syndrome, to more subtle disturbances, such as blunted adrenal stress responsiveness, which are generally *subclinical*. They include not only acute or chronic toxicological processes (such as alcoholic pancreatitis) or side effects (such as opioid-associated hypogonadism) that are *incidental* to the addiction process but also perturbations of endocrine and neuroendocrine function, inherited or acquired, that are *intrinsic* to the pathophysiology of addiction. Not only are endocrine systems affected by psychoactive drugs, but they respond in ways that can contribute to the development and maintenance of addiction.

Addiction has famously been said to "hijack" limbic-hypothalamic hedonic motivational pathways that normally subserve basic biological functions including feeding and sexual behaviors (Olsen 2011). Disturbances of appetitive and metabolic regulation are emerging as an area of commonality or overlap between addiction to psychoactive drugs and "food addiction." Sexual dysfunction (dealt within the ▶ Chap. 109, "Sexual Function and Alcohol and Other Drug Use") is common in people with substance use disorders, and while the etiology is often complex and multifactorial, endocrine dysfunction may play a role, especially with opioids and alcohol.

In this chapter, we present both *clinical* endocrine disorders associated with the use of alcohol and other drugs and *subclinical* endocrine disturbances, taking endocrine systems in turn to support a broad conceptual understanding. While preclinical studies are considered, the main focus is on human studies.

The aim is to foster the recognition and appropriate management of clinical endocrine disorders and also appreciation of subtle endocrine effects that underpin acute and chronic withdrawal and relapse, better to inform counseling of patients

and the understanding of laboratory tests, and making the reader aware of potential therapies arising out of the rapidly increasing body of knowledge in this area.

108.2 Hormones and Addiction

108.2.1 The HPA Axis

Clinically manifest disorders of the hypothalamic-pituitary-adrenal (HPA) axis related to alcohol and other drug use are uncommon. By contrast, abnormalities in stress responsiveness, including but not limited to the HPA axis, are increasingly recognized as central to the pathophysiology of addiction syndromes. For heroin and as was later shown other drugs including cocaine and alcohol, cycles of intoxication and withdrawal were found to be associated acutely with stimulation of the HPA axis and chronically to dampened or blunted HPA reactivity to various experimentally testable physical and emotional stressors. By the 1970s, evidence of the improvement of these disturbances in opiate addicts receiving methadone maintenance treatment (MMT) led to two hypotheses: that it was the cycle of short-acting drug-induced changes rather than the action of opioids per se that led to changes in stress responsiveness and that the fluctuating conditions of repeated intoxication with opioids had endocrine effects that were more pronounced than under the relatively state of opioid receptor occupancy in MMT, during which a large proportion of opioid receptors remain unoccupied and hence available to perform their normal physiological functions (Kreek et al. 2002; Zhou et al. 2010).

Although the earliest evidence of HPA axis perturbations accrued in relation to opioids, and much information is available from animal studies of stimulants, overall the greatest body of information is available in relation to alcohol, albeit mainly in men. While there is evidence that HPA axis disturbance may precede problematic alcohol use in some people, alcohol intoxication and cycles of withdrawal both acutely stimulate the HPA axis, and chronic exposure leads to blunted HPA reactivity (Richardson et al. 2008).

The effects of addictive substances on stress response systems are seen at the level of the hypothalamus (corticotrophin-releasing factor, CRH), the anterior pituitary (adrenocorticotropic hormone, ACTH), and the adrenal gland (glucocorticoids – cortisol in humans). They are modulated by signaling molecules in the brain including the endogenous opioids β-endorphin and dynorphin (Bruchas et al. 2010; Sarkar 2012), which exert a tonic inhibition of ACTH reversible by naloxone, neuropeptide Y (Gilpin 2012), leptin, and orexin/hypocretin (Shalev et al. 2010). In response to stress, CRH not only regulates the HPA axis via the pituitary but acts in extrahypothalamic (limbic) areas of the extended amygdala to modulate its emotional consequences.

It has been postulated that activation of the HPA axis by stressful emotional states is a homeostatic process in which diurnal and metabolic signals are "superseded by signals from the limbic system and prefrontal cortex" (Lovallo 2006).

A chronically activated and response-blunted stress response system is postulated to contribute to vulnerability to stress-related and cue-related relapse, to the negative reinforcement which marks the shift from impulsive to compulsive behavior in the development of alcohol dependence (Koob 2013). However, dysregulation of the HPA axis may be related to the current level of alcohol consumption rather than dependence per se (Boschloo et al. 2011). Abnormalities in HPA stress responsiveness persist into, but eventually improve with, alcohol abstinence (Coiro et al. 2007). Elevation of brain glucocorticoids persisting after alcohol withdrawal may contribute to chronic cognitive impairment seen in recovering alcoholics (Rose et al. 2010), and stress-related craving has been associated with poorer alcohol treatment outcomes (Higley et al. 2011).

Similar HPA axis disturbances have been documented with cocaine (Zhou et al. 2010), cannabis (Somaini et al. 2012), benzodiazepines (Heberlein et al. 2008), MDMA (Wolff et al. 2012), and to a lesser extent amphetamines (Uhart and Wand 2009). A relationship has also been shown between elevated cortisol and cognitive impairment in cocaine dependence (Fox et al. 2009).

While tobacco smoking produces acute dose-related effects on HPA hormones, endocrine effects of tobacco cessation are reported as modest (Pickworth and Fant 1998).

Abnormal glucocorticoid responsivity to stress is also associated with depression (Penninx et al. 2013) and with post-traumatic stress disorder (PTSD) with and without alcohol dependence (Brady et al. 2006).

Genetic, prenatal, and early developmental environmental factors play a role in disturbed HPA axis regulation in people with substance dependence. Thus alcohol exposure in utero (Weinberg et al. 2008), in utero cocaine and methamphetamine exposure (Kirlic et al. 2013), prepubertal trauma and chronic stress (Enoch 2011), and childhood neglect (Somaini et al. 2011) have all been implicated in abnormalities in HPA tone later in life. On the other hand, family history of alcohol dependence or heavy alcohol use has not been consistently been associated with cortisol levels or glucocorticoid responsivity (Mick et al. 2012; Huizink et al. 2009; Hardin and Adinoff 2008).

108.2.1.1 Clinical Issues

By contrast with the subclinical HPA disturbance in addiction, overt adrenal dysfunction is relatively uncommon. Among the so-called pseudo-Cushing's syndromes, depression and alcohol use are important causes. Frank hypercortisolism can rarely be caused by excessive alcohol use (Besemer et al. 2011), which is reversible upon alcohol abstinence. The differential diagnosis is difficult, as cortisol may fail to suppress on low-dose dexamethasone suppression tests, and midnight serum or salivary cortisol tests may give false positives; the dexamethasone/CRH suppression test is more specific; specialist consultation is usually required. Alcohol use itself can cause a false-positive result on 24 urinary cortisol assessments (Vilar et al. 2007).

Hypercortisolism has not been reported for other drugs. However, there are case reports of adrenal insufficiency in people using chronic opioids for pain, including

fentanyl (Oltmanns et al. 2005), tramadol, hydromorphone, and methadone, and it is reversible on cessation of opioid. It is unknown how commonly this occurs in people on maintenance treatment for opioid dependence. Untreated adrenal insufficiency can be fatal, and treatment with corticosteroids can improve quality of life where opioid use needs to continue.

A further important diagnostic consideration is the adrenal insufficiency of acute illness (Arafah 2006). Additionally chronic liver disease, in the addiction medicine context most commonly due to alcoholic liver disease or chronic viral hepatitis, can lead to HPA hyporesponsiveness, which in the case of cirrhosis is not related to its etiology (Zietz et al. 2003).

Arising out of animal or small human studies, several possible therapeutic interventions for stress response systems have been proposed as showing promise for the treatment of alcohol dependence. These include the alpha adrenergic blocker prazosin for reducing stress- and cue-induced craving (Fox et al. 2012), the glucocorticoid receptor antagonist mifepristone which in rats prevented escalation of alcohol intake and compulsive responding to alcohol vapor (Vendruscolo et al. 2012), CRF receptor antagonists (Logrip et al. 2011), and the beta adrenergic blocker propranolol which reduced operant alcohol-reinforced responding in rats (Gilpin and Koob 2010). It has been proposed that measures such as cortisol and cortisol/corticotropin (ACTH) ratio may help predict risk of relapse (Sinha 2011). Naltrexone and acamprosate may have effects to prevent the decline of ACTH and cortisol during early alcohol abstinence (Kiefer et al. 2006).

Awareness of possible lifelong neurohormonal effects of in utero exposure to drugs and alcohol should inform counseling for pregnant women and other women of childbearing age.

108.2.2 Gender, Sex Hormones, and Addiction

There is large evidence of sexually dimorphic responses to addictive substances in animals and humans. Broadly speaking, men are at higher risk of alcohol dependence and have higher rates overall of drug use, and women are at higher risk for initiation, a "telescoped" trajectory to dependence for most drugs studied, and have higher rates of relapse (Carroll and Anker 2010). While these differences reflect to some extent social and cultural factors and may reflect pharmacokinetic factors such as lower lean body weight, smaller liver size, and slower metabolism, especially with alcohol and cannabis (Fattore et al. 2009), sex hormonal factors have a role, from puberty on (Kuhn et al. 2010).

The higher risk for males of alcohol dependence (Lenz et al. 2012) appears to be related in part to the actions of testosterone itself. Preclinical studies, and to a lesser extent human studies, suggest also estrogen may facilitate drug use, while progesterone may be protective, attenuating responses to cocaine, alcohol, and nicotine (Anker and Carroll 2010; Lynch and Sofuoglu 2010). Progesterone treatment increased ratings of negative subjective effects and decreased ratings of positive

effects from nicotine in smokers (Sofuoglu et al. 2009). Both progesterone and testosterone reduced cocaine self-administration in female rhesus monkeys, supporting previous evidence that progesterone may be a protective factor (Mello et al. 2011).

There are differences according to female hormonal status: acute doses of alcohol reduced progesterone levels in women both using and not using oral contraceptives (OCs), while only women on OCs showed increases in estrogen levels and there appears little effect of alcohol on these hormones in postmenopausal women (Sarkola et al. 1999; Longnecker and Tseng 1998). The relationship of smoking behaviors to estradiol and progesterone in women is complex, varying over the menstrual cycle and specifically with the ratio of progesterone to estradiol (Schiller et al. 2012).

It is proposed that sex hormones act throughout life causing both *transient* and also *permanent* ("organizational") effects on the brain, such that in utero and early childhood, exposure to sex hormones can contribute to the risk of developing alcohol dependence (Lenz et al. 2012). Additionally, alcohol and cocaine exposure in utero can increase HPA tone throughout later life, and this phenomenon is also sexually dimorphic (Weinberg et al. 2008; Chaplin et al. 2010).

108.2.2.1 Clinical Issues

Accumulating evidence that progestins mitigate or modify and alter the effects of cocaine, alcohol, and nicotine in humans, while conversely drugs can increase progestin levels, suggests a role of progestins in homeostatic response to drug effects and possibilities for their therapeutic use in addiction (Anker and Carroll 2010; de Wit 2011).

In recently abstinent smokers, gender differences in the reinforcing effects of nicotine appear related to differential availability of the β(2)*-nicotinic acetyl chlorine receptor, which was correlated with progesterone levels in female smokers; the authors suggest potential relevance for the effectiveness of nicotine receptor-mediated smoking quit therapies in women (Cosgrove et al. 2012). Blunted HPA axis reactivity associated with alcohol dependence was, surprisingly, not found in a study of abstinent women (Adinoff et al. 2010), raising the possibility that this effect is sexually dimorphic; this may have a bearing on the finding that long-acting injectable naltrexone for alcohol dependence was not significantly effective for women (Garbutt et al. 2005). Women have heightened pain perception and pain-related distress compared with men, for reasons including psychological coping style and possibly hormonal milieu: studies suggest the importance of menstrual cycle phase and a U-shaped relationship of estrogen with pain experience (Paller et al. 2009).

More research is needed into the treatment implications of gender-based differences in drug use initiation, craving and relapse, and the possibility of gender-specific interventions. Similarly, clinicians might consider that stage of menstrual cycle may be important in relation to quit and relapse from drugs and alcohol, though much more research is needed into this phenomenon before specific inferences can be drawn for clinical practice.

108.2.3 Disturbance of the HPG Axis and Gonadal Hormones

Psychoactive substance-related disturbances of the hypothalamic-pituitary-gonadal (HPG) axis are most prominently related to alcohol and opioid use. While alcohol has complex actions including direct toxic effects on the gonads, liver disease, and central nervous system opioid effects, by contrast, the action of opioids is mainly through their action on opioid receptors.

As with the HPA axis, changes in the HPG axis were extensively investigated in the early day of MMT. Hormonal changes and related clinical manifestations, including hypogonadism in males and menstrual irregularities in women, were found to be common in heroin addiction and generally, gradually, to improve with MMT (Schmittner et al. 2005; Kreek et al. 2002; Zhou et al. 2010). Nonetheless varying degrees of hypogonadism have been shown to be prevalent in men receiving MMT (Bliesener et al. 2005; Hallinan et al. 2009) and men receiving opioids for chronic pain, in which case it is more clearly treatment emergent (Daniell 2002). In cross-sectional studies, men on buprenorphine maintenance have not had lower testosterone levels than controls, but a case series of buprenorphine-associated hypogonadism shows that this can occur (Bliesener et al. 2005; Hallinan et al. 2009; Colameco and Zimmerman 2008).

Ample evidence attests to the potential of chronic opioid use to cause hypogonadotropic hypogonadism, in both men and women, owing to opioid-mediated increase of tonically inhibitory hypothalamic dopaminergic tone. In women this may include both low estradiol and testosterone levels; the mechanism of the latter may include suppressed adrenal androgen production (Daniell 2008).

Both cannabis and alcohol use reduce luteinizing hormone (LH) secretion, partly mediated in both cases by cannabinoid type 1 receptors at the level of the hypothalamus. However, neither cannabis nor tobacco smoking has been consistently associated with hypogonadism in humans; indeed male tobacco smokers have been found to have higher testosterone levels than nonsmokers (Brown and Dobs 2002; Blanco-Munoz et al. 2012), and tobacco smoking was associated with higher levels of adrenal androgens in women (Daniell 2006). Nor is there evidence of hypogonadism associated with cocaine.

Symptoms of hypogonadism may be relatively specific, such as hypoactive sexual desire, erectile dysfunction, and reduced sperm quality and quantity in men and hypomenorrhea, amenorrhea, and other menstrual irregularities in women. Less specific clinical features include low mood and energy, loss of muscle strength and mass, and osteoporosis, in both sexes.

Dehydroepiandrosterone sulfate (DHEAS) deficiency has been reported in pregnant women on methadone maintenance during pregnancy, relative to controls (Facchinetti et al. 1986), and in men and women chronically using sustained-action prescribed opioids (Daniell 2006). DHEA and its sulfate are the most abundant steroid hormones in humans and are primarily of adrenal origin (but also from the fetus in pregnant women). Their production is ACTH and probably CRH dependent, and the mechanism of opioid-associated deficiency may be CRH inhibition. DHEAS deficiency is associated with similar symptoms to testosterone

deficiency. The prevalence and clinical importance of DHEAS deficiency in opioid-dependent people require further investigation.

Hypogonadism associated with heavy alcohol use is found in both men and women and with liver cirrhosis of whatever cause (Kaymakoglu et al. 1995). Women with cirrhosis related to alcohol and other causes commonly develop amenorrhea which frequently shows low LH and intact response to gonadotropin-releasing hormone, indicating a hypothalamic rather than pituitary cause (Bell et al. 1995). In men several mechanisms are at work including impaired LH binding to Leydig cells, reduced testicular steroid hormone formation, and actions of alcohol at the level of the hypothalamus (Van Steenbergen 1993).

Male hypogonadism and the commonly, but not universally, associated signs of feminization with liver cirrhosis appear to be multifactorial, with elevated estradiol, DHEAS, and serum hormone-binding globulin (SHBG) and reduced free and total testosterone concentrations commonly found, and these changes related to Child's cirrhosis grade; the hypogonadism appears to be of hypothalamic origin (Kaymakoglu et al. 1995; Handelsman et al. 1995). Both hormone changes and sexual dysfunction were reported to be more severe in cirrhotics where alcohol was the cause (Bannister et al. 1987).

Heavy chronic alcohol use also causes hypogonadism in the absence of severe liver disease. Ethanol intoxication and withdrawal in males are associated with low androgen levels and elevated SHBG, and these tend to improve with abstinence (Iturriaga et al. 1999). Male alcoholics during withdrawal showed low mean levels of testosterone and SHBG, with elevated follicle stimulating hormone (FSH) and LH declining during recovery (Ruusa et al. 1997). About a third of male alcoholics were hypogonadal at the beginning of withdrawal management, while 1 in 5 developed hypogonadism during withdrawal, the majority recovering slowly over time (Kruger et al. 2006). A group of young male heavy alcohol users were found to have low mean plasma testosterone with both low LH and FSH, suggesting hypothalamic/pituitary impairment and evidence of impaired antioxidant function, which could impair function of Leydig and Sertoli cells (Maneesh et al. 2006).

Studies of gonadal hormone testing in relation to alcohol use in women have given heterogenous results, probably reflecting menstrual cycle phase and menopausal status, acute versus chronic effects of alcohol, presence or absence of liver and other disease, and clinical versus population samples. Low testosterone, elevated estradiol, and decreased FSH in premenopausal women have been reported in women drinking alcohol, though inconsistently (Verkasalo et al. 2001). Half of a group of 30 alcoholic women showed low progesterone and a third had low LH during early withdrawal; in addition to HPG suppression and alcohol-induced increase in prolactin, toxic effects of alcohol on the ovaries are suggested to explain these findings (Augustynska et al. 2007).

108.2.3.1 Puberty

In animal studies, alcohol consumption can delay female puberty (Dees et al. 2009), but few studies are available for the effect of prepubertal drug and alcohol use in humans. Girls who used alcohol before puberty had four times the odds of delayed

puberty compared with nonusers; more modest effects of alcohol and tobacco were noted in delayed breast development (Peck et al. 2011).

While several studies have shown early menarche to be associated with higher risk of initiation of substance use and of alcohol abuse, possibly reflecting psychosocial and hormonal factors, a large Canadian population study has not found alcohol, tobacco, or other drug use to be associated with age of menarche (Al-Sahab et al. 2012). Early puberty may be associated with higher levels of later substance use because the adolescent risk period is entered at a younger age (Patton et al. 2004).

108.2.3.2 Human Fertility

There have been fewer studies of the effects of alcohol and other drugs on fertility in women than in men. Alcohol reduces sperm quality and quantity both through reduced testosterone and direct toxic effects on the Sertoli cells of the testes, but is not associated with male infertility in population-based studies or infertility clinic samples (La Vignera et al. 2013). Sperm quality has been shown in two studies to be impaired in heroin users and men on MMT, though no information was provided on tobacco or alcohol use in these studies; it is possible that this improves on MMT when there is no additional heroin use (Ragni et al. 1988; Cicero et al. 1975). Tobacco smoking was associated with reduced sperm quantity and quality in men and impaired fertility in women, in a recent literature review (Sadeu et al. 2010), but this was not the case for other drugs studied. There is modest evidence for a negative effect of cannabis on sperm concentration and morphology in men (Kolodny et al. 1974), and a case control study of women with primary infertility showed significantly increased risk of ovulatory infertility in women who had recently smoked cannabis (Mueller et al. 1990; see Brown and Dobs 2002) for a review of preclinical evidence regarding cannabis and fertility). Tobacco use is a possible confounder in clinical studies of cannabis and fertility; most cannabis smokers also use tobacco.

In a case control study of women with infertility, odds ratio for ovulatory infertility were 1.3 (95 % CI 1.0, 1.7) for moderate and 1.6 (95 % CI 1.1, 2.3) for heavier alcohol drinkers, compared with nondrinkers (Grodstein et al. 1994). A prospective study of couples planning first pregnancy found dose-related lower rates of conception among women drinking alcohol (Jensen et al. 1998). By contrast a large prospective population study did not find alcohol use (or caffeine use) to be associated with reduced ovulatory fertility after adjusting for confounders including parity (Chavarro et al. 2009), which may reflect low prevalence of higher alcohol use in this sample.

Anovulation or oligoovulation can be reasonably inferred from menstrual disturbance including amenorrhea. Treatment emergent amenorrhea is common in women treated with opioids for chronic pain. It is common for menstrual periods to return even after prolonged amenorrhea in methadone-treated heroin users (Schmittner et al. 2005). Ovulation can occur despite amenorrhea in opioid-dependent women.

Testosterone and anabolic-androgenic steroids are available on prescription for medical indications, including wasting associated with AIDS and with chronic corticosteroid use. They are also commonly available off prescription and used

by sportsmen to improve performance and "body builders" to increase muscle bulk and strength. Anabolic-androgenic steroid dependence is now a recognized entity, described as developing in about 30 % of AAS users, and appears to involve endogenous opioid and mesolimbic dopaminergic pathways. There are similarities to other substance dependence syndromes including continued use despite awareness of harms and a withdrawal syndrome, albeit mild, on a par with nicotine. There are also differences including low dependence liability compared with other drugs and the relative lack of intoxication, euphoria, or other immediate psychoactive reinforcement but rather psychological reinforcement in terms of body image and other desired effects (Hildebrandt et al. 2011).

108.2.3.3 Clinical Issues

Chronic pain is common in opioid-dependent people and in alcohol-treatment-seeking populations, both of which groups may be at risk of hypogonadism. Although the relationship between chronic pain and alcohol use has been little studied, it is likely that dependence may arise out of self-medication of chronic pain with alcohol, as also with opioids, including over-the-counter and illicit sources. Pain sensitivity may be increased in hypogonadism, and there is some evidence for therapeutic benefit of estrogens and testosterone in hypogonadal states and post-menopausal women, for improving pain management (Daniell 2002, 2008).

While an opioid dose relationship with hypogonadism has not been consistently demonstrated in cross-sectional studies, this may reflect interindividual variation in opioid tolerance and pharmacokinetics. In practice, hypogonadism and its symptoms commonly abate with reduced opioid dose or weaning. Opioid rotation may facilitate reduction of opioid load, as may use of non-opioid pain medications and therapies. Men on MMT might benefit from transfer to BMT: this may amount to an opioid dose reduction as buprenorphine is a partial agonist opioid.

The place of hormone replacement for opioid treatment-related hypogonadism is not clearly established in guidelines (Katz and Mazer 2009). However, in some cases, hormone replacement may be indicated where opioid therapy is required long term, whether for chronic pain or opioid dependence, and where symptoms of hypogonadism are onerous or are affecting treatment adherence (Daniell 2002; Hallinan et al. 2009). Several studies suggest low testosterone in males to be a risk factor for suicidality (Sher 2002). The benefits of androgen replacement in HIV-infected men with hypogonadism are well established (Ponte et al. 2009).

Diagnosis of opioid-related hypogonadism in women can be made on the basis of amenorrhea or oligomenorrhea with or without menopausal symptoms, earlier in life than the expected menopause, with low estradiol and testosterone levels but normal or low FSH and LH (in contrast to the postmenopausal state, where FSH and LH are raised).

In men the diagnosis of hypogonadism is relatively straightforward. Owing to pulsatile and diurnal variability of testosterone levels, assays should be performed on morning samples and on more than one occasion. Clinicians should bear in mind that there may be a degree of acute opioid dose-related suppression of testosterone and time blood tests accordingly. Published guidelines for a threshold for androgen

supplementation treatment vary from total testosterone 6.8 nmol/L (200 ng⁄dl) to 10.4 nmol/L (300 ng⁄dl), but most recommend about 8 nmol/L (230 ng⁄dl) (Smith and Elliott 2012). Measurement of total testosterone may suffice (Conway et al. 2000). Measurement of gonadotropins (LH and FSH) enables distinction between primary and secondary (hypogonadotropic) hypogonadism. In the case of the latter, FSH and LH are low or normal, indicating the lack of an appropriate pituitary response to low testosterone. In this case the possibility of pituitary disease, most commonly a pituitary adenoma or hemochromatosis, requires measurement of other pituitary hormones including prolactin and TSH and iron studies.

Given the established risk of osteoporosis in hypogonadal men and women (including postmenopausal women) and the established benefits of hormone replacement to preserve and even improve bone density, bone densitometry should be performed if available, where hypogonadism is persistent, especially where there are other risk factors such as chronic liver disease (see Sect. 108.2.7).

The decision whether or not to treat hypogonadism depends on an assessment of whether it appears symptomatic (low mood, energy, muscle strength, sexual dysfunction), whether the person is likely to benefit from hormone replacement, possible side effects and contraindications (in men these include obstructive sleep apnea, structural heart disease, and prostatic cancer – prostate-specific antigen surveillance and digital rectal prostatic examination are indicated), and the acceptability of alternative management including reducing opioid doses. It may be considered inappropriate to prescribe hormone replacement where there is ongoing problematic alcohol or illicit opioid use. In the absence of randomized controlled trials of androgen replacement for opioid-related hypogonadism, treatment decisions should be made on an individual basis.

Treatment of hypogonadism in women is generally some form of hormone replacement with estrogen with or without progestins in oral, transdermal, or intravaginal forms depending on the symptoms being treated and potential side effects including possibly increased risk of breast cancer and atherosclerotic disease (Katz and Mazer 2009). There is little evidence for testosterone supplementation in hypogonadal women except for hypoactive sexual desire (see ▶ Chap. 109, "Sexual Function and Alcohol and Other Drug Use").

Impaired sperm production and persistent hypogonadism are possible consequences of use of pharmaceutical androgens or anabolic steroids, whether prescribed or nonprescribed, but most described cases involve nonprescribed use of supra-therapeutic doses. The implications for male fertility of androgen replacement for hypogonadism or wasting states are unclear. It is suggested that any assessment of androgenic steroid use should include consideration of persistent consequences upon cessation of their use (Tan and Scally 2009).

Although benefits of DHEAS replacement treatment for deficiency states have been demonstrated for other conditions including depression, the place of DHEAS replacement in opioid-dependent people requires further investigation.

There are high rates of unplanned pregnancy in substance-dependent populations. Given that menstrual periods can return even after prolonged amenorrhea in substance users, especially with stabilization of opioid-dependent women on opioid

pharmacotherapy and with abstinence in alcohol-dependent women, it is important to consider issues of contraception in counseling and medical practice in this population.

Given the strong evidence for reduced fertility with tobacco smoking, and the more modest evidence suggested risk attributable to alcohol and cannabis, it is prudent to recommend cessation of these substances where fertility is a problem.

108.2.4 Prolactin, Gynecomastia, Oxytocin, and Addiction

Mesolimbic dopaminergic pathways are central to the reinforcement of most addictive substances. Dopamine also acts in the tuberoinfundibular pathway as a prolactin inhibitor. There is, as with steroid hormones, evidence that prolactin is stress responsive and plays an important modulating role in the pathogenesis of addiction for several substances. For example, there is evidence of a negative correlation of serum prolactin and craving in women during alcohol withdrawal (Hillemacher et al. 2005) and of increased prolactin reserve in alcoholics during withdrawal (Basile et al. 1981).

Endogenous oxytocin is emerging as playing a central role in "empathogenic" effects of MDMA and GHB. Alcohol also stimulates release of oxytocin from the posterior pituitary, and in animals oxytocin administration can prevent development of tolerance to ethanol and opiates and self-administration of methamphetamine (Rettori et al. 2010; McGregor and Bowen 2012).

Frank hyperprolactinemia is associated with the use of numerous medications, including antidopaminergic agents such as antipsychotics, as well as with alcohol. There are case reports of hyperprolactinemia in alcoholic men and women, and animal studies suggest the mechanism to involve both increased prolactin release and stimulation of lactotrope growth in the anterior pituitary (Sarkar 2012). Cannabinoids, by contrast, inhibit prolactin release (Rettori et al. 2010), and there is no reported association of cannabis use with hyperprolactinemia (Brown and Dobs 2002).

Heroin users have been found to have acutely elevated prolactin levels, which appears to normalize with MMT where, in contrast to opioid treatment for chronic pain, clinically relevant hyperprolactinemia is uncommon in the absence of liver disease (Kreek et al. 2002; Hallinan et al. 2009; Moshtaghi-Kashanian et al. 2005; Trajanovska et al. 2013; Rhodin et al. 2010).

Cocaine is reported as causing acute suppression but chronic elevation of prolactin; while chronic cocaine users had higher prolactin levels than controls, elevation outside normal ranges was uncommon, and prolactin levels also do not predict treatment response (Walsh et al. 2009; Patkar et al. 2004) (Gorelick and Wilkins 2006). Chronic methamphetamine users during abstinence had higher prolactin levels than controls (Zorick et al. 2011), but clinical hyperprolactinemia has not been reported for amphetamine use.

Prolactin elevation may be asymptomatic or be associated with amenorrhea and other menstrual disturbances, sexual dysfunction, galactorrhea, and gynecomastia. The relationship between gynecomastia and hyperprolactinemia is complex.

Both gynecomastia and hyperprolactinemia may occur in chronic liver disease: suggested mechanisms include gynecomastia-inducing properties of prolactin and altered estrogen/androgen ratios.

Gynecomastia may occur without hyperprolactinemia, and while prolactin levels have been reported as higher in men with gynecomastia, there appears to be no relationship between prolactin levels and gynecomastia in cross-sectional studies of people with liver disease (Farthing et al. 1982). Grun (1985) reported the prolactin levels of cirrhotic women to be no higher than controls, suggesting that cirrhosis per se does not cause hyperprolactinemia. Farthing et al. (1982) found progesterone was raised in 72 % of men with liver disease, suggesting a possible causative role for progesterone in gynecomastia in this context. Men with alcoholic liver disease had increased circulating levels of androstenedione compared with men with idiopathic hemochromatosis, in whom gynecomastia is rare (Kley et al. 1985).

Animal studies suggest maternal alcohol consumption can interfere with prolactin and oxytocin function during lactation and in non-lactating women (see Heil and Subramanian (1998) for a review). Moderate doses of alcohol reduced milk production and ejection in lactating women, and lactating women with a family history of alcoholism were shown to have a blunted prolactin response to breast stimulation and an alcohol challenge (Mennella and Pepino 2010).

108.2.4.1 Clinical Issues

Hyperprolactinemia in the absence of an obvious cause will usually prompt investigation for a possible pituitary adenoma, which involves at least the assessment of other pituitary hormonal function and examination of visual fields. Where there is a high probability of it being related to drugs, the clinician may feel it is not necessary to perform expensive (CT, MRI) imaging studies of the pituitary fossa. A plain X-ray of the pituitary fossa is seldom helpful.

Hyperprolactinemia is commonly asymptomatic but can be associated with anovulation and oligo- or amenorrhea and causes reduced milk production in lactating women. It is considered a cause of sexual dysfunction (see ► Chap. 109, "Sexual Function and Alcohol and Other Drug Use"). Where hyperprolactinemia is symptomatic with the use of psychoactive drugs, dose reduction or discontinuation may be necessary.

The probability diagnosis of gynecomastia in men with chronic liver disease or heavy alcohol use should generally be tested with ultrasound imaging and hormone profiling, as breast cancer in men and prolactin-secreting adenomas are important diagnoses which should not be missed. Galactorrhea may uncommonly be associated with methadone use, as may gynecomastia, which may improve with dose reduction. In this connection, Krause (2012) advises caution in attributing causality where there is association: neither methadone in particular nor opioids in general, nor amphetamines, are statistically significantly associated with gynecomastia in the published literature.

When measuring prolactin levels in people on MMT, it should be borne in mind that an acute opioid dose-related elevation of prolactin, though diminished, persists in MMT (Bart et al. 2003). Blood testing should be timed accordingly.

Trials of intranasal oxytocin in conditions manifesting deficits in social behavior, including autism and schizophrenia (De Berardis et al. 2013; Domes et al. 2013), have shown early promise, and some hopes are held for oxytocin for addiction treatment, especially in amphetamine dependence, specifically for social deficits seen with narrowing of the behavioral repertoire and neglect of nondrug-related activities (McGregor and Bowen 2012).

Information about the presence of alcohol in breast milk and possible consequences of alcohol for production of breast milk is important for counseling against alcohol use by breast feeding women.

108.2.5 Thyroid Function and Addiction

With the exception of alcohol and tobacco, thyroid disturbance is not commonly reported as arising from use of addictive substances. Methadone-maintained patients showed elevations of total T3, T4, and thyroxin-binding globulin compared with controls; however, free T3 and T4 and thyroid-stimulating hormone (TSH) were normal, confirming the clinically euthyroid condition of subjects. These and similar changes reported in heroin users changes likely represent changes in thyroid binding globulin and are generally not significant clinically (Kreek et al. 2002). Neither cannabis nor psychostimulants have been associated with increased prevalence of thyroid disorders.

Tobacco smoking is a risk factor for Graves disease and Graves ophthalmopathy (Stan and Bahn 2010; Asvold et al. 2007), and this risk reduces on tobacco cessation. Smoking also appears to reduce thyroid autoantibodies and reduce risk of hypothyroidism (Asvold et al. 2007; Mehran et al. 2012). The mechanisms may involve tobacco constituents other than nicotine.

Several lines of animal research converge to suggest a possible role of the hypothalamic-pituitary-thyroid (HPT) axis in the neurobiology of alcohol dependence, including craving, withdrawal, and relapse (Rasmussen 2003; Hashimoto et al. 2011).

In humans, most studies have assessed alcoholics during withdrawal or abstinence rather than ongoing drinking; liver disease, depression, stress, and other drug use are confounders for assessing thyroid function in alcoholics. Blunting of the TSH response to thyrotropin-releasing hormone (TRH) has been a common finding, and this often persists into abstinence (Hermann et al. 2002). Measurement of T4 and T3 during alcohol withdrawal have given highly variable results, which may reflect confounding factors including liver disease, changes in assays, effects of withdrawal treatment, and heterogenous trait and state psychological conditions within the study populations (Ozsoy et al. 2006). Liappas et al. (2006) have reported normalization of thyroid function tests after alcohol withdrawal and correlation of thyroid hormones and mood. A toxic effect of alcohol on the thyroid, with reduced thyroid hormone production causing chronically elevated TRH and downregulation of TRH receptors, is posited as a unifying mechanism for these various effects (Hermann et al. 2002).

Relationships between alcohol craving and free T3 (direct) and TSH (inverse) have been demonstrated in alcohol-dependent patients treated with baclofen (Leggio et al. 2008).

108.2.5.1 Clinical Issues

Addiction medicine clinicians should be alert to the possibility of thyroid disorders and to the wide range of possible causes in their patient populations. Hypo- and hyperthyroidism are standard differential diagnoses where there are comorbid mood or anxiety disorders.

Both subclinical and clinical hypothyroidism have been associated with clinical depression and cognitive impairment and may increase the relapse risk among alcoholics. It has been suggested that subclinical hypothyroidism can contribute to cognitive impairment and depression which may diminish capacity for alcohol abstinence (Hermann et al. 2002; Sher 2002). FT3 levels were elevated and correlated with number of traumatic events and increased arousal in soldiers with PTSD both with and without alcohol dependence (Karlovic et al. 2004).

Clinicians should bear in mind that calcitonin levels may be elevated in chronic alcoholism (Vantyghem et al. 2007) and by tobacco smoking (d'Herbomez 2011) which can cause confusion in diagnosis and follow up of medullary thyroid cancers.

108.2.6 Appetite Factors, Obesity, Diabetes, and Addiction

There is emerging evidence of the involvement of several appetitive hormones not only in the intake of food but also in the neurochemistry of substance dependence, especially in alcohol dependence and craving. In the central nervous system (CNS), these include the satiety factor leptin and orexin, which is appetite-stimulating. Derived from the gut, circulating peripherally but also active in the CNS, is the appetite-stimulating peptide ghrelin.

Leptin and ghrelin are involved in the hypothalamic regulation of energy homeostasis and also integrated at the level of the hypothalamus with prolactin and ACTH, thereby connecting appetite regulation with the HPA axis (Wurst et al. 2007), with mesolimbic reinforcement pathways, and with the orexigen neuropeptide Y (Leggio et al. 2011).

Ghrelin, which is increased by physiological stress (Schellekens et al. 2012), was positively correlated with alcohol craving in men in early abstinence (Koopmann et al. 2012) and is important in alcohol reward (Leggio et al. 2011). In animal models, leptin appears important in mediating dopaminergic reward for alcohol, cocaine, and amphetamines (Jerlhag et al. 2010). While leptin plasma concentrations correlated positively with nicotine craving in withdrawing tobacco smokers, orexin plasma concentrations correlated negatively with nicotine craving (von der Goltz et al. 2010). Orexin is released into the VTA in response to several drugs (Borgland et al. 2010) and was strongly positively correlated with alcohol withdrawal symptoms (von der Goltz et al. 2011).

Much interest centers on neurohormonal commonalities of substance dependence and "behavioral addictions," especially food addiction (Grosshans et al. 2012; Volkow et al. 2013). Food-induced activation in human mesolimbic reinforcement pathways was found to be correlated with plasma concentration of leptin (Grosshans et al. 2012). Smokers with pathological eating behavior had evidence of raised leptin levels (Koopmann et al. 2011).

Insulin resistance and leptin resistance are both hallmarks of obesity, leptin resistance apparently contributing to food craving (Pandit et al. 2011). Insulin signaling modulates effects of drugs on dopamine neurotransmission in human mesolimbic reinforcement pathways, providing a link between the "metabolic milieu" and hedonic centers for feeding: the clinical relevance of this for addictive substances remains to be elucidated (Daws et al. 2011).

Endogenous opioids, mainly though the mu-receptor, also play a role in promoting motivation for food intake (Olszewski and Levine 2007). Weight gain is common during methadone maintenance treatment, and while this is commonly an increase from a status of low body mass index (BMI) or underweight in people using illicit opioids, towards normality (Okruhlica and Slezakova 2012), obesity does develop in some people on MMT (Szpanowska-Wohn et al. 2004). One year of MMT normalized the decreased serum leptin (but not the decreased serum adiponectin and increased resistin concentrations) found in 12 heroin addicts compared with controls (Housova et al. 2005).

Like heroin users, stimulant users are commonly underweight. Amphetamine was widely prescribed in the 1950s and 1960s as obesity treatment, especially in the USA, and dependence commonly ensued. Of interest is the fact that cocaine- and amphetamine-regulated transcript (CART), an endogenous psychostimulant neuropeptide shown to mediate some exogenous psychostimulant-related behaviors, is also a satiety factor.

In utero exposure to tobacco smoking is associated with obesity later in life (Lisboa et al. 2012). Tobacco smokers have lower BMI than controls but higher abdominal adiposity, largely accountable by lifestyle differences, but heavier smokers have higher BMI than lighter smokers; all smokers are at risk of weight gain on cessation (Pisinger and Jorgensen 2007). Both tobacco smoking and nicotine replacement treatments are associated with insulin resistance (Chang 2012), and this like obesity is a risk factor for type 2 DM. Despite the known effects of cannabis to increase appetite, a large general population study has found prevalence of obesity to be lower in cannabis users than in nonusers (Le Strat and Le Foll 2011).

The association of alcohol with body weight, obesity, and related complications is complex. There is some evidence that low-level and frequent alcohol use may have a protective effect against obesity, compared with nondrinking, whereas higher-level and binge-style drinking increases the odds of overweight and obesity (Arif and Rohrer 2005). A large prospective study of Caucasian men showed alcohol consumption to be unassociated with central obesity, negatively associated with incidence of the metabolic syndrome and HDL concentrations, and positively associated with higher fasting glucose concentrations (Stoutenberg et al. 2013).

Number of weekly drinking occasions was found to be a risk factor for obesity independent of total alcohol intake (Dumesnil et al. 2013). In another large community study, moderate-to-high consumption of alcohol and of beer and spirits was associated with later development of high waist circumference, whereas moderate-to-high wine consumption appeared to have the opposite effect (Vadstrup et al. 2003). Acute alcohol intake increases insulin resistance, but chronic alcohol use has a U- or J-shaped relationship, with insulin resistance and prevalence of metabolic syndrome increasing with alcohol intake over 40 g/day in men and probably less in women; hepatic steatosis may have a role in this insulin resistance (Alkerwi et al. 2009; Ramirez et al. 2013).

Most of the apparent benefit of low-dose alcohol use in reducing risk of coronary heart disease is thought to be related to beneficial effects on cholesterol – with reduced LDL and increased HDL. However, heavier alcohol use is associated with elevations of triglycerides and hypertension, with increased risk of coronary heart disease and mortality from other causes.

108.2.6.1 Clinical Issues

Chronic alcohol use tends to worsen hyperglycemia and may worsen insulin resistance, being thus a risk factor for type 2 diabetes mellitus (T2DM). The metabolism of alcohol via the alcohol dehydrogenase pathway depletes the body of nicotinamide adenine dinucleotide (NAD), which is necessary for gluconeogenesis. Consumption of alcohol in a fasting state can contribute to risk of hypoglycemia, in both diabetics and nondiabetics, owing to impaired gluconeogenesis and reduced cortisol and growth hormone response to hypoglycemia. Such hypoglycemia may respond poorly to therapeutic glucagon injection, owing to depletion of liver glycogen stores.

Heavy alcohol use can cause ketoacidosis in both diabetic and nondiabetic people, especially T2DM, owing a combination of insulin resistance, decreased gluconeogenesis, fasting and depletion of glycogen, and dehydration. This ketoacidosis is usually nonhyperglycemic and beta-hydroxybutyrate predominates over other ketones (Umpierrez et al. 2000), which can lead to negative results on standard ketone tests of serum and urine.

Recent cocaine use has been reported associated with increased risk of diabetic ketoacidosis (DKA), owing to a combination of poor treatment adherence and possibly metabolic effects of catecholamines (Nyenwe et al. 2007). There are case reports of DKC associated with MDMA use (Gama et al. 2010); however, this has not been reported for amphetamines.

Chronic hepatitis C is associated with increased risk of diabetes mellitus and insulin resistance, which reciprocally are associated with more rapid HCV disease progression and poorer outcomes from interferon-based treatments (Badar et al. 2012). Both acute and chronic alcoholic pancreatitis may progress to diabetes mellitus; tobacco smoking is also independently associated with chronic pancreatitis (Law et al. 2010).

For diabetics using insulin or oral hypoglycemic agents, poor adherence to medications, neglect of nutrition, and unawareness of the warning signs of hypoglycemia that may result from use of psychoactive drugs, especially but not only

alcohol, are often harmful and dangerous. Hypoglycemia of whatever cause, including frank malnutrition, and preference for simple sugars or alcohol over complex carbohydrates can also lead to symptoms closely resembling anxiety and panic, which should be borne in mind in evaluating patients who appear to "self-medicate" anxiety with psychoactive drugs.

Metformin and troglitazone are potentially dangerous where there is hepatic impairment, as for instance with alcoholic liver disease or chronic viral hepatitis in injection drug users.

While recovery from underweight is welcome, development of overweight and obesity on MMT is of concern, especially given the high prevalence of chronic HCV in this population and the additional risk of hepatic steatosis. Dietary deficiencies including high proportion of total energy derived from sugar and low dietary fiber have been identified in women on MMT (Zador et al. 1996) and are likely to contribute to risk of obesity and diabetes as well as the unpleasant but under-recognized symptoms of chronic constipation.

Weight gain after tobacco smoking cessation and independently increased risk of T2DM are important clinical problems, especially in people who use other drugs and/or alcohol, for whom smoking may be a "last remaining pleasure" but the greatest health risk. Weight gain is common after people quit tobacco smoking and can be a common reason for failure to quit or relapse after quitting. While they are used, bupropion, fluoxetine, NRT, and varenicline all reduce the weight gain of smoking cessation, but the effect is not demonstrably sustained; only exercise interventions show convincing benefit (Farley et al. 2012).

The nexus of addictive and appetitive factors is nicely illustrated by the case of cannabinoid antagonists (rimonabant and taranabant), which have been trialed rather for weight reduction and smoking cessation, than for treatment of cannabis dependence (possibly reflecting the more substantial commercial possibilities of pharmacotherapies for these indications). Sadly, safety issues have limited the development of cannabinoid antagonists to date.

Among other potential therapies in the future, it is suggested that ghrelin antagonists might affect alcohol-seeking behavior (Leggio 2010); leptin has been proposed as a potential treatment for obesity; in an animal study, the unselective opioid antagonist naltrexone decreased both hedonic and incentive types of motivation, where the μ-selective antagonist GSK1521498 decreased only incentive motivation, suggesting its potential usefulness as a possible treatment of binge eating (Giuliano et al. 2012).

108.2.7 Bone Metabolism

Use of a number of psychoactive drugs appears to increase risk of disorders of bone metabolism, principally osteopenia and osteoporosis. A challenge for the epidemiologist in understanding causation and the clinician in treating these conditions is that drug exposures and other risks including liver disease, dietary deficiency, poor exercise, and sunlight exposure are commonly multiple in the one person.

From population-based studies, including twin studies, the risk of tobacco smoking for osteoporosis is unequivocal: risk is greatest for reduced bone mineral density (BMD) at the hip, is greater in men than women, is less in premenopausal women, increases with age and total exposure, and decreases eventually with smoking cessation; fracture risk is also increased, independently of BMD (Ward and Klesges 2001). Lower bone mineral density has been shown in adolescent girls who smoke before menarche (Lucas et al. 2012) and was evident in young male military recruits who smoked tobacco, despite their relatively short smoking histories (Eleftheriou et al. 2013). Mechanisms that have been proposed include reduced calcium absorption, effects of smoking on weight – increased body weight short of marked obesity being generally protective against osteoporosis – and altered estrogen production and metabolism (Wong et al. 2007).

Evidence for alcohol is more equivocal. Like smoking, heavy alcohol use is identified as highly prevalent in men presenting with osteoporosis (Peris et al. 2008), but meta-analyses of population-based studies suggest a J-shaped association of increasing alcohol consumption with fracture risk and a positive linear relationship with mineral bone density, i.e., alcohol may increase risk of falls but be protective against osteoporosis (Berg et al. 2008). Population studies however may not capture risk of higher-level alcohol use. High rates of vertebral fractures and low bone density have been identified in alcohol-dependent men and women (Clark et al. 2003; Peris et al. 1995). Osteoporosis is common in people with severe liver disease (Monegal et al. 1997; Uretmen et al. 2005), but where there is no liver disease or hypogonadism, mineral bone density in men with alcohol dependence has not consistently differed from controls and generally not in women (Malik et al. 2009; Odvina et al. 1995). Unaccounted factors including nutritional status, smoking, and amount of alcohol used might explain these inconsistencies.

Several mechanisms have been proposed to explain the range of effects of alcohol on bone, from increased estrogen levels protecting bone with moderate alcohol use to oxidative stress and impaired osteoblast activity with heavier drinking. Among the more consistent findings have been low serum vitamin D and the bone formation marker osteocalcin in heavy alcohol users. Among postmenopausal low-level alcohol users, abstinence from alcohol increased and resumed alcohol use decreased osteocalcin and the resorption marker C-terminal telopeptide, suggesting that alcohol inhibits bone turnover in this female population (Marrone et al. 2012). The osteopenic state in alcoholism is characterized by decreased bone formation and remodeling rather than increased bone resorption and remodeling as occurs with hypogonadism (Chakkalakal 2005). Several studies suggest the reversibility of changes in bone formation markers and bone density with prolonged abstinence.

Two studies have reported low BMD in methamphetamine users compared with controls: Japanese prison convicts measured at the calcaneus by Achilles ultrasound bone densitometer (Katsuragawa 1999) and hospitalized Korean methamphetamine users assessed by DEXA (Kim et al. 2009a); neither study controlled for other major causes of reduced bone density. BMD was assessed in a baseline cohort of 210 HIV-negative men who have sex with men as part of an HIV prophylaxis trial: the

use of amphetamines (OR = 5.9) and inhalants (OR = 4.6) was significantly associated with low BMD (Liu et al. 2011). There are no published studies of the specific effects of cocaine on bone metabolism in humans, nor for cannabis. Preclinical research of interest includes the role of the cocaine-amphetamine-related transcript (CART) in bone metabolism and the role of cannabinoid CB2 receptors, which are expressed in osteoblasts and osteoclasts: the CNR2 gene which encodes CB2 is associated with low bone mineral density in women (Bab et al. 2009).

Low BMD has been reported in users of chronic opioids in a number of settings. In people treated with opioids for chronic pain, hypogonadism is an important treatable cause of osteoporosis (Fortin et al. 2008). Low bone density has been reported in recent heroin users in two studies (Pedrazzoni et al. 1993; Wilczek and Stepan 2003): former heroin addicts did not differ from controls, and after a year of methadone maintenance, osteoresorption and osteoformation markers, though not bone density, normalized. Also a majority of patients (74 %) on injectable heroin maintenance treatment were found to have low bone mineral density (Dursteler-MacFarland et al. 2011).

Osteoporosis was reported in 35 % and osteopenia in 48 % of MMT patients in Boston, a high latitude North American city, with male gender, lower weight, and heavy alcohol use significantly associated with lower BMD, and high prevalence (52 %) of low vitamin D in the same MMT population, for which black or Hispanic ethnicity was a risk factor (Kim et al. 2006, 2009b). Mean BMD was also low for men, but not women, on MMT in New Zealand (Grey et al. 2011). These studies have used reference ranges or populations rather than control groups for BMD. Three studies comparing people with HIV with HIV-negative people at risk of HIV have found methadone treatment to be an independent risk factor for lower BMD in men and women and for decline in BMD in women (Arnsten et al. 2006, 2007; Sharma et al. 2011); other risk factors included HIV seropositivity, HCV seropositivity, older age, non-black race, lower body weight, postmenopausal status, age, and tobacco smoking.

108.2.7.1 Clinical Issues

In populations using alcohol and other drugs, comprehensive assessment and management should involve attention to issues of bone health. This may involve screening for osteoporosis using dual-energy X-ray absorptiometry (DEXA) where available; insurance cover for these tests may be limited. Among evidence-based indications for screening are hypogonadism, chronic liver or kidney disease, and previous pathological fractures. While hypogonadism, tobacco smoking, and alcoholism are reported as independent risk factors for secondary osteoporosis in males, none of these emerged supported in a recent meta-analysis for an American College of Physicians guideline for DEXA screening (Liu et al. 2008).

While vigilance for osteoporosis in people treated with chronic opioids, including methadone, is suggested, there are no generally accepted guidelines for who should have DEXA, gonadal hormone testing, or vitamin D testing in these populations. Screening should probably be targeted rather than universal, considering all of the potential risk factors identified above (Fortin et al. 2008).

It is prudent to carry out vitamin D testing in high-risk populations, such as men and women who have limited sun exposure for reasons of dress culture or lifestyle and people with darker skin pigmentation especially those living at high latitudes. However, this test is expensive, highly subject to assay and seasonal variability, and probably not needed to assess response to treatment. It may be more practicable in many cases – without testing for deficiency – to counsel adequate sunlight exposure and recommend vitamin D supplementation where this is not feasible or sufficient.

Management of actual, or risk of, low bone density should be comprehensive, including support for smoking cessation and moderation of alcohol use, calcium supplementation, increase of physical activity, and attention to dietary issues, especially where there is low body weight (Mosekilde et al. 2013). Treatment may include testosterone replacement for hypogonadal males; however, it should be borne in mind that low bone mineral density was commonly seen in men treated with opioids for chronic pain who had normal testosterone (Fortin et al. 2008). Similarly, an early menopausal state in women on chronic opioids may prompt consideration of hormone replacement therapy.

Where there is osteoporosis, antiresorptive agents including the bisphosphonates, the selective estrogen receptor modulators and denosumab, and bone-forming agents including parathyroid hormone and teriparatide may be used subject to all the usual considerations for safety and cost-effectiveness.

108.2.8 International Perspectives

As with many areas of medicine and public health, research into endocrine manifestations of addictive disorders has been greatest in Western societies, though there have been substantial contributions from East Asian countries and, in the case of opioid use, countries of the Middle East, especially Iran, albeit mainly for men.

Reflecting this, information is best for drugs commonly used in Western societies, especially alcohol, opioids, cannabis, cocaine, and amphetamines. Even in those societies, information is scant for drugs, such as inhalants, used by the most marginalized groups. Information is almost entirely lacking for some types of drug use common in other cultures, such as khat, kava, coca chewing, or inhalant use.

On the other hand, research from Western multicultural and multiethnic cultures, especially from the USA, does provide some reassurance about commonalities across ethnic groups for endocrine effects of major drug classes. In general one might suppose that endocrine processes are likely to be broadly similar across ethnicities, but this remains supposition in the absence of specific research, which remains to be done.

Further, there are clear sociocultural and ethnic difference in risks of certain endocrine problems common in users of AOD, especially diabetes mellitus and metabolic syndrome, vitamin D deficiency and its complications, access to expensive investigations (such as DEXA) or treatments, and prevalence of AOD risk factors for endocrine disease, the awareness of which must inform appropriate public health and clinical interventions to reduce harms and improve quality of life.

108.3 Conclusion

Endocrine manifestations of addictive disorders and their treatments are probably more often subclinical than clinically overt and requiring treatment. Understanding the range and scope of these potential endocrine effects has the benefit of helping the clinician maintain vigilance for clinically important disturbances when they occur. It can underpin a broad understanding of hormonal and neurohormonal factors that predispose to and perpetuate addiction and of emerging research directions for treatments. It can provide an important counterpoint to perceptions that addiction is a moral failing or weakness of the will: sometimes our patients, even more than their critics, need to be reminded of how *physiological* the process of addiction is.

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Sexual Function and Alcohol and Other Drug Use

109

Richard Hallinan

Contents

Abstract

Alcohol and other drugs have actions in limbic-hypothalamic hedonic motivational pathways that normally subserve basic biological functions including sexual behaviors. They may also have a range of other physiological and psychological effects on sexual function.

Psychoactive drugs are often used to facilitate or enhance sexual behaviors, but they can also cause sexual dysfunction. Their use can be associated with risky or harmful sexual behaviors.

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Pharmacotherapies commonly used in addiction treatment, including opioid pharmacotherapies, sedative/hypnotics, antidepressants, and antipsychotics, can negatively affect sexual function, with implications for treatment adherence and effectiveness. Further, common psychological and physical comorbidities in people with substance use disorders may cause sexual dysfunction.

An understanding of these issues can help clinicians working in the field of addiction better to appreciate motivations for continuing or reducing drug use, can inform motivational and harm reduction interventions, and can improve understanding of issues around treatment adherence. While there are challenges for clinicians in speaking about sexuality with their patients, they are an important part of comprehensive assessment and treatment planning. The clinical benefits of addressing these issues, ranging from reducing sexual risk behavior to improving quality of life of people receiving pharmacotherapies, can be substantial.

109.1 Introduction

The impact of alcohol and other drugs on human sexuality can be considered across three domains: the deliberate use of alcohol and drugs to facilitate or enhance sexual behaviors, their association with risky or harmful sexual behaviors, and their association with sexual dysfunction (Palha and Esteves 2008).

Despite much research, there remain difficulties in comprehensively describing the effects of alcohol and other drugs (AOD) on human sexual function. Human sexuality and its disorders are complex and multifactorial. There remain uncertainties even in the definitions of normality and dysfunction in human sexuality, with sexuality differing greatly between males and females, and across the human lifespan; conceptions of normality vary too across cultures. One must distinguish between acute effects and chronic effects in heavy or dependent users of alcohol and other drugs.

Epidemiologically, moreover, there are three distinct types of study populations for AOD-related sexual dysfunctions: clinical populations with sexual dysfunctions, clinical populations with substance use disorders, and population studies, which generally shed light only on commonly used substances.

109.2 Substances and Sexual Dysfunction

109.2.1 Models and Neurochemical Substrates of Normal Sexual Function

In order to understand the effects of alcohol and other drugs on sexual function, and to identify and manage sexual dysfunction where it occurs, it is important to have an idea of what is normal.

Since Masters and Johnson in the 1960s, and with various amendments (Kaplan, Lief, and Levine, among others), the human sexual response has been described as

proceeding in linear fashion through phases of desire, excitement, orgasm, and resolution. Progressive editions of DSM correspondingly defined disorders of reduced or impaired desire, arousal, and orgasm, adding premature ejaculation (PE) in the case of men and dyspareunia and vaginismus in women; ICD 10 broadly resembles DSM-IV in this respect.

However, the linear model has been challenged for women, and a cyclic, interconnected model proposed instead, with overlap between phases, especially desire and arousal, and reflecting the complexity of sexual motivation, the importance of intimacy, and a broader view of sexual satisfaction. In men too desire and arousal may not be so easily separated (Brotto 2010). In the move toward DSM-V, the merging of desire and arousal disorders, incorporation of a polythetic approach, recognizing subtypes of arousal disorder, refining criteria of distress and duration, and addition of hypersexual disorder are currently debated (Brotto 2010; Segraves 2010; Reid et al. 2012).

Estimates of the typical frequency of sexual activity derived from the work of Kinsey in the USA appear unduly sanguine in the light of more recent population studies, and it is unlikely that experiences in "Western" societies can be simply extrapolated to other cultures.

A current model for sexual responsiveness in mammals including humans posits a dynamic balance of excitatory and inhibitory forces, across all domains of sexual function (Pfaus 2009). Notwithstanding substantial heterogeneity, there are also important commonalities among the neurochemical substrates of reward and reinforcement of the essential biological functions of feeding and sexual activity, and those of drugs and alcohol, most clearly increased dopamine activity in the nucleus accumbens (Lajtha and Sershen 2010; Olsen 2011).

Sexual excitatory factors include dopaminergic pathways which control attention to incentive stimuli, behavioral responses, and parasympathetic outflow to genital areas; melanocortin; the "bonding hormone" oxytocin; and noradrenaline, which has an "inverted U"-shaped relationship with sexual behavior, whereby states of fear or anxiety reduce excitation. There are complex interplays among these factors, and their tone is set hormonally by estradiol and testosterone and also by gonadotropins directly. Testosterone is important for sexual desire and arousal in both men and women, and estrogen in arousal in women, including genital swelling and lubrication. Peripherally these hormones modulate mechanisms involving nitric oxide synthase, vasoactive peptides, prostaglandins, and serotonin, which act to increase genital blood supply (Pfaus 2009).

The evolutionary value of inhibition of mammalian sexual function is likely dual: to allow refractory periods and to avoid conflict within the species. Inhibition can be divided into two aspects, satiety and executive (prefrontal) inhibition. Evidence from the feeding literature suggested serotonergic mediation of satiety. Opioids may have a dose-related rewarding function, inducing satiety at higher doses. Endocannabinoids also appear to have a role in sedation after orgasm. Sedation in itself is likely to play a role in sexual responsiveness.

To these ideas of incentive, reward, satiety, and sedation might be added the more general idea, from addiction studies, of salience, as exemplified by the neglect of essential biological functions (feeding, exploration, and copulation) in animal models of addiction.

The central role of dopaminergic, serotonergic, and opioid-mediated processes in normal human sexuality points to the potential effects of prescribed and nonprescribed psychoactive substances in human sexuality.

109.2.2 How Common Is Sexual Dysfunction? Evidence from Population Studies

Meta-analysis of population studies suggests high prevalences of sexual *difficulties* in women and men. Approximately two thirds of women report *difficulty* with sexual desire, one third difficulty with orgasm, one third difficulty with arousal, and a quarter of sexual pain, with wide ranges around these estimates (Hayes et al. 2006). However, only a proportion of the women were distressed by these difficulties, and symptoms were often not persistent; probably fewer women meet DSM or IDS criteria for sexual disorders (Segraves and Woodard 2006). Difficulties with erection are reported by 30–40 % of men, with premature ejaculation 10–20 % and delayed orgasm less common. These relative prevalences are reflected in frequency of clinical presentation for sexual dysfunction (Nobre et al. 2006).

In general, while prevalence of sexual difficulties increases with age in both men and women, associated distress declines with age (Derogatis and Burnett 2008). Only a proportion of older men with ED are concerned about it (Corona et al. 2010). Erectile dysfunction (ED) and PE however can be common even in young men (Mialon et al. 2012). Similarly, older women report increasing levels of low libido with age, but the percentage who are distressed by this remains unchanged across the age groups (West et al. 2008).

109.2.3 Deliberate Use of Psychoactive Substances in Sexual Behavior

Nonclinical population studies show that drugs and alcohol are commonly used deliberately and strategically for sex-related purposes, with differences among drugs in their perceived effects and uses: cocaine often to prolong sex, alcohol to facilitate encounters, and MDMA to increase desire, closeness, and satisfaction but which may reduce erection and delay orgasm (Zemishlany et al. 2001; McElrath 2005; Bellis et al. 2008). Opiate users are less likely than other drug users to attribute positive sexual effects to their drug (Rawson et al. 2002). Amphetamine and cocaine are most commonly reported to be pro-sexual, but some people may report the opposite. Both perceived effects and expectancies about drug use are largely heterogenous, varying demographically and by gender, especially for cocaine (Rawson et al. 2002). Women may believe or perceive effects of drugs in men to be different from their own

(El-Bassel et al. 2003), and the perceived effects of drugs and alcohol may be context dependent, with the impact of cocaine being largely mediated by social context of use.

Some evidence suggests the use of drugs as deliberate enhancement of sexual function or as self-medication for sexual difficulties (mainly premature orgasm but also arousal difficulties), with sexual difficulties an important factor in the initiation of drug use (La Pera et al. 2008; Mintz et al. 1974). Oral erectile dysfunction agents are commonly used by recreational and dependent users of alcohol and illicit drugs to increase sexual pleasure or performance and may be a marker for sexual risk among gay men (Prestage et al. 2009).

109.2.3.1 Alcohol, Drugs, and Sexual Risk Behaviors

Recreational drug use has been associated with high rates of unprotected sex (Riley et al. 2001; McElrath 2005). Stimulant users are reported as having higher numbers of sexual partners, higher rates of providing sex for money or drugs, and higher rates of sexual risk behavior (Molitor et al. 1999; Lejuez et al. 2005; Weatherby et al. 1992). Disinhibition and impulsivity may underpin increased risk behaviors. While overall alcohol use may be associated with sexual risk behavior among women, data do not support increased occasion by occasion risk (Beckman and Ackerman 1995; Taylor et al. 1999).

While sedative/hypnotics and GBH are sometimes implicated in "date rape" cases, by far the most common identified substance is alcohol (Palha and Esteves 2008).

109.2.4 Understanding the Etiology of Sexual Dysfunction

Assessment and management of sexual dysfunction in any clinical context requires understanding of its multifactorial origins.

109.2.4.1 Hormonal Factors

In women, testosterone and DHEAS peak in early adulthood and decline rapidly and progressively after that so that levels are halved by age 40 (Davison and Davis 2011). By contrast, decline of testosterone in men is progressive from about age 40. Men have 10–16 times the level of testosterone compared to women, so the slow decline with age does not impact on hormonal drive and libido until much older ages.

Androgen deficiency is common in men presenting with ED (Kohler et al. 2008) and androgen replacement has benefit for sexual function in hypogonadal men (Bhasin et al. 2007, 2010), though not for the normal testosterone decline of aging. A large population-based cohort of older men showed no association of testosterone or sex hormone-binding globulin (SHBG) and erectile dysfunction, except in men with increased luteinizing hormone (LH) levels suggesting primary testicular disease (Kupelian et al. 2006).

Although androgen deficiency has not been unequivocally associated with female sexual dysfunction, several studies have shown benefit of testosterone therapy on sexual desire, arousal, orgasm, and satisfaction in naturally or surgically menopausal women (Davison and Davis 2011). There remains a challenge in

understanding changes with menopause as distinct from aging itself; declining estrogen after menopause is the cause of vaginal dryness and dyspareunia (Dennerstein and Hayes 2005). Postmenopausal status increased the risk of sexual dysfunction in middle-aged women, while postmenopausal hormone replacement use was protective (Chedraui et al. 2009).

Hyperprolactinemia and hypothyroidism are also causes of sexual dysfunction in both genders. While hyperprolactinemia commonly manifests with sexual dysfunction, hyperprolactinemia is an uncommon cause of male sexual dysfunction and is not necessarily mediated by reduced testosterone (Buvat 2003; Bhasin et al. 2007).

109.2.4.2 Vascular and Neural Factors

Normal sexual function requires intact vascular and neural function to the genital areas. Neuropathy may include autonomic or reduced tactile sensation, especially in genital areas. Endothelial disease (Braun et al. 2000) is a common cause of ED in men. Sexual dysfunction in diabetes is probably mediated by both vascular disease and neuropathy and multiple sclerosis through neuropathy.

109.2.4.3 Bodyweight, Obesity, Sleep Apnea, and Exercise

Overweight and obesity are increasingly implicated as risk factors for male sexual dysfunction, principally ED (Shamloul and Ghanem 2013). ED prevalence was threefold high among men aged 20–45 years with obesity (Andersen et al. 2008). ED has a U-shaped relationship with weight (Cheng and Ng 2007), that is, underweight is also a risk factor. Janiszewski and Janssen et al. (2009) reported in a large general male population, abdominal obesity and physical inactivity were associated with erectile dysfunction independent of body mass index. Physical activity itself appears protective against ED in cross-sectional studies (Cheng and Ng 2007).

Obstructive sleep apnea is also independently associated with ED (Budweiser et al. 2009) as it disturbs REM sleep, which is the time during sleep when most nocturnal erections occur. Fewer nocturnal erections are a factor in the development of chronic diffuse corporeal fibrosis, leading to ED. This is preventable with early CPAP.

109.2.4.4 Other Medical Illnesses

Numerous other medical illnesses can cause sexual dysfunction. Chronic liver disease, especially liver failure, is related to sexual dysfunction independent of alcohol use (Durazzo et al. 2010). Also illnesses affecting general constitution and fitness, such as chronic heart disease and lung disease.

109.2.4.5 Psychological Factors

Distress from sexual dysfunction appears to be not only age but relationship dependent, in both genders. Postmenopausal status and presence of sexual dysfunction in the male partner increased risk of sexual dysfunction in middle-aged women, while partner faithfulness and menopausal hormone replacement use were protective (Chedraui et al. 2009). In men, self-esteem and depression mediate the effect of erectile dysfunction on quality of life (Ponizovsky 2008). Continued alcohol use by alcohol-dependent

men has negative impacts on sexual intimacy in the relationship which improved with abstinence (Nirenberg et al. 1990). Marital conflict may be an important factor in reported sexual dysfunction in male alcoholics (O'Farrell et al. 1997).

109.2.4.6 Psychiatric Disorders and Their Treatment

A key issue is distinguishing between preexisting and treatment-emergent sexual dysfunction in people with mood (dysthymia and major depression), anxiety (especially posttraumatic stress, social anxiety/phobia, and obsessive-compulsive disorders), and psychotic disorders, in whom psychotropic medications are used. In each of these groups of disorders, there are high rates of sexual dysfunction, generally in the direction of hypofunction (Clayton and Balon 2009). Anxiety and depression are also associated with PE in men (Quek et al. 2008). As with opioid pharmacotherapies (see below), sexual emergent side effects can affect psychiatric treatment adherence (Serretti and Chiesa 2011).

While SSRIs appear mainly to affect orgasm, and antipsychotics primarily desire, all phases of sexual function can be affected by psychotropic medications. Controlled studies are best for antidepressants, including tricyclic and SSRIs, and for antipsychotics. There appears to be a hierarchy among antidepressants regarding treatment-emergent sexual dysfunction with prevalences ranging from 25 % to 80 %. Among SSRI/SNRIs, on meta-analysis sertraline, venlafaxine, and citalopram have higher prevalence of sexual dysfunction than escitalopram and fluvoxamine. Several other types of, primarily non-serotonergic, antidepressants (including agomelatine, bupropion, moclobemide, mirtazapine, and nefazodone) do not significantly differ from placebo (Gregorian et al. 2002; Serretti and Chiesa 2009).

Sexual dysfunction is also common in people treated with antipsychotic agents, with no significant difference found between risperidone, quetiapine, and olanzapine (Nagaraj et al. 2009); these drugs may also be associated with hyperprolactinemia. Although hyperprolactinemia and sexual dysfunction were both common in men on second-generation antipsychotics, they were not correlated with each other (Johnsen et al. 2011).

For benzodiazepines and mood stabilizers, evidence is relatively lacking in humans (Labbate 2008; Clayton and Balon 2009). Benzodiazepines, including diazepam, clonazepam, and alprazolam, have been associated with treatment-emergent male sexual dysfunction (Fossey and Hamner 1994).

109.2.5 Sexual Dysfunction Related to Substance Use and Dependence

109.2.5.1 Tobacco and Cannabis

In men, tobacco smoking is clearly related to risk of vasculogenic ED, which may be atherogenic, and the risk appears to be cumulative with packet years of smoking and persist in former smokers (Tengs and Osgood 2001; Millett et al. 2006; Chew et al. 2009). ED may occur despite higher LH and testosterone in

current smokers (Corona et al. 2005). Evidence is lacking for specific effects of tobacco smoking on arousal in women, though other risks/indicators of endothelial disease (metabolic syndrome, obesity, diabetes, and coronary heart disease) are associated with female sexual dysfunction (Miner et al. 2012).

Daily cannabis use has been associated in one study with difficulty achieving orgasm in men, but not sexual dysfunction in women (Smith et al. 2010); in another with inhibited orgasm and dyspareunia (Johnson et al. 2004). Other studies have shown benefits of cannabis for erectile function (Shamloul and Bella 2011). The effects of cannabis use on sexual function are hard to disentangle from those of tobacco, as tobacco is often mixed with cannabis when the latter is smoked, and where cannabis is used in other ways than smoking, tobacco smoking is typically also common.

109.2.5.2 Alcohol

Moderate alcohol use in men has been found in several cross-sectional studies to confer protection from ED (Bacon et al. 2003; Chew et al. 2009; Millett et al. 2006). A meta-analysis (Cheng and Ng 2007) also reported a protective association for alcohol and ED, even at levels 80 g/day and higher. However, in two large Chinese population studies, even moderate alcohol use was associated with increased risk of ED (Lee et al. 2010). Among midlife women, alcohol intake (along with older age and vaginal dryness) was associated with lower levels of passionate love for the partner (Tomic et al. 2006).

Heavy alcohol use and alcohol dependence are common in populations with sexual dysfunction (Fagan et al. 1988; Haro et al. 2006). Alcohol-dependent men have been reported in several studies in a wide range of countries to have sexual dysfunction including premature ejaculation, ED, and reduced desire (Mandell and Miller 1983; Fahrner 1987; Arackal and Benegal 2007; Dissiz and Oskay 2011). Sexual dysfunction is also reported for alcoholic women, though evidence is less (Jensen 1984). In the absence of severe liver disease or hypogonadism, male sexual dysfunction improves with abstinence (Schiavi et al. 1995; Van Thiel et al. 1983).

Pach and Szurkowska et al. (2007) found high prevalence of erectile dysfunction in alcohol-dependent men: this was not associated with total testosterone and prolactin concentrations, though gonadotropin levels were significantly higher in the group of men with erectile dysfunction, consistent with a toxic effect of ethanol on the testes.

Autonomic neuropathy commonly goes unrecognized in alcoholics and appears to be dose related and potentially reversible on abstinence; in heavy male alcohol users, erectile dysfunction may be the only symptom of parasympathetic neuropathy (Villalta et al. 1989; Monforte et al. 1995; Ravaglia et al. 2004).

109.2.5.3 Opioids

Chronic users of opioids including heroin, and opioid pharmacotherapies for dependence and for chronic pain, have high prevalence of sexual dysfunction, consisting in hypoactive sexual desire and arousal difficulties in both genders, and increased ejaculatory latency in men (Pfaus and Gorzalka 1987; Daniell 2002).

There is good evidence for both treated and untreated opioid-dependent men, including numerous studies in heroin users from a range of countries and cultures (Hallinan et al. 2008; Bang-Ping 2009) and several studies of opioid substitution treatment (Bliesener et al. 2005; Hallinan et al. 2008; Quaglio et al. 2008; Nik Jaafar et al. 2013). Erectile dysfunction appears to be less common in men on buprenorphine than on methadone, though it must be noted these were not randomized treatment populations (Bliesener et al. 2005; Hallinan et al. 2008). The evidence is less strong for women than men; what published evidence there is also supports reduced sexual interest, emotional arousal, and orgasm satisfaction in women on MMT compared with controls (Teusch et al. 1995).

Several studies from the early days of methadone maintenance treatment (MMT) addressed this issue in opioid-dependent women and men, suggesting either improvement or little change from prior heroin use (Wieland and Yunger 1970; Garbutt and Goldstein 1972). Garbutt and Goldstein prospectively studied 120 entrants into MMT, and while average "climax" and "impotence" scores improved at 27 weeks, compared with baseline, the majority of the 30 % who dropped out of treatment reported loss of sexual function as a major reason. More recent studies of men on MMT and BMT have given mixed results for ED with opioid pharmacotherapy showing improvement (Babakhanian et al. 2012; Cioe et al. 2013), deterioration (Zhang et al. 2011), or no change (Chen et al. 2012) compared with prior heroin use. By contrast with heroin users entering opioid pharmacotherapy, where prior sexual dysfunction is common, sexual dysfunction in men treated with opioids for chronic pain is more clearly "treatment emergent" (Daniell 2002).

Cross-sectional studies of the relationship between methadone dose and sexual dysfunction have given mixed results, the majority finding no association (Crowley and Simpson 1978; Teusch et al. 1995; Hallinan et al. 2008; Nik Jaafar et al. 2013; Brown et al. 2005). However, this may not reflect the impact of opioid dose in any individual, owing to large interindividual variation in the pharmacokinetic and pharmacodynamics of methadone; and clinical experience is that methadone dose reductions often improve sexual dysfunction (Espejo et al. 1973; Teusch et al. 1995; Mintz et al. 1974). Similarly, relationship between testosterone levels and erectile dysfunction has sometimes, but not consistently, been shown in cross-sectional studies of opioid users (Cioe et al. 2010).

Most reported studies identifying orgasmic difficulties in men do not show the direction of the dysfunction: commonly used and convenient research tools such as the IIEF and the Arizona Sexual Experiences Scale (ASEX) do not distinguish between PE and delayed orgasm. Where it has been studied, premature ejaculation is found to be much more common in men using heroin and on methadone treatment than in general community studies, and opioids may be used deliberately by some men to manage this problem (Al-Gommer et al. 2007; Chekuri et al. 2012). There is conflicting evidence on whether the PE precedes opioid use, one study suggesting that PE may be a factor in the initiation of illicit drug use (La Pera et al. 2008).

While opioid antagonists have been trialed as treatment for erectile dysfunction, and prima facie one would expect their use in treatment of opioid dependence would eliminate opioid-related sexual dysfunction, the only study available of sexual

dysfunction in men on naltrexone maintenance treatment found high rates of erectile dysfunction, comparable with those on buprenorphine maintenance, consistent with the multifactorial etiology of sexual dysfunction in opioid-dependent men. However, PE was the most common dysfunction in these men (Ramdurg et al. 2012).

109.2.5.4 Stimulants

In clinical populations with substance use disorders, cocaine use is commonly associated with impaired sexual, especially orgasmic, function (Cocores et al. 1988; Kim et al. 1992; Henderson et al. 1995; Rawson et al. 2002; Kopetz et al. 2010) but also reduced sexual desire and performance (Weatherby et al. 1992).

Primary dependent (mostly oral) amphetamine users in treatment had also had high rates of sexual dysfunction, though less than those of dependent opiate, mostly injecting, users (Gossop et al. 1974).

Bang-Ping et al. (2009) reported IIEF scores of 721 men in a compulsory drug treatment facility, interviewed shortly after their entry into treatment. All IIEF domains scored significantly lower than controls for the substance users, whose ED prevalence overall was 36 %. Odds ratios for ED were significantly higher relative to controls for heroin (4.8) and amphetamines (3.2) but not for MDMA users. 47 % of heroin users reported reduced sexual desire, while 28 % of ATS users did so; 23 % of ATS users reported increased sexual desire; however, the sexual desire scores of this subgroup were still significantly lower than controls. The heterogenous nature of actual or perceived drug effects is further reflected in the fact that about half of the men in this study reported increased, while about 15 % decreased, ejaculatory latency.

109.2.6 Clinical Assessment and Management of Sexual Dysfunction in People with Substance Use Disorders

Fundamental to the assessment of sexual dysfunction in people with substance use disorders is consideration that there may be several contributing factors. These include:

1. The actions of the substances themselves
2. Psychiatric and medical comorbidities, as described above
3. The psychosocial context including partner status, self-esteem, and relationship issues
4. The effects of treatments, especially with dopamine antagonists, serotonergic agents, and opioids, but also non-psychotropic medications such as beta-blockers, antihistamines, NSAIDS, and thiazide diuretics (Clayton and Hamilton 2010).

Few patients may volunteer information about the impact of substance-related sexual disturbance on their lives. Most men with treatment-emergent sexual problems on MMT had not mentioned their concerns owing to embarrassment (Hanbury et al. 1977). Furthermore, low sexual desire may not constitute a symptom – if anyone complains it may be the partners. Clinical presentation

may also be indirect, with depression, relationship problems, under-dosing or poor treatment adherence with opioids and other medications, and even dropping out of treatment.

Clinicians can develop skills to incorporate inquiry about sexual matters as part of comprehensive assessment and ongoing assessment in a way that puts patients at their ease. For example, it may be helpful to inquire about sexual dysfunction as one of other common medication-associated symptoms: in the case of opioids, these include sweating, constipation, and disturbances of menstruation.

It should be clarified which phases of sexual response are involved, desire, arousal, and orgasm, as this may determine the focus of management. Also important in assessment is the effect that sexual dysfunction is having on their lives, and whether it is affecting their attitude to treatment in any way. Unless there is distress, sexual dysfunction may not need specific management.

For people continuing to use drugs or alcohol, discussion of sexual function may be important in motivational interventions. Abstinence may come at a perceived or actual cost to one's sex life; equally, sexual dysfunction resulting from alcohol or drug use may be a salient motivation toward abstinence (Palha and Esteves 2002). Sexual contexts, cues, and triggers may be important for risk of relapse, to be considered in relapse prevention strategies (Rawson et al. 2002).

Where "self-medication" of premature ejaculation with alcohol or other drugs is causing problems, discussion of alternatives might reduce harms and risk of dependence or relapse. The SSRIs fluoxetine, paroxetine, and citalopram, and also tramadol, have shown benefit for treatment of premature ejaculation, though tramadol may not be effective longer term (Alghobary et al. 2010; Dadfar and Baghinia 2010; Wu et al. 2012). Their use for the indication of PE is off-label; recently the short-acting SSRI dapoxetine has been approved in a number of countries specifically for the indication on PE. Other treatments include local anesthetics such as topical lignocaine and the Masters and Johnson "squeeze technique" which usually involves participation of the partner.

Drug treatment services and other settings where brief intervention can be carried out provide opportunities for discussing drug-related sexual risks and promoting safe sex.

There is little specific evidence to guide *treatment* of sexual dysfunctions arising out of substance use and its disorders. In the absence of such evidence, the clinician must integrate more general evidence into clinical practice.

109.2.7 The Example of Opioid Pharmacotherapy

Where sexual dysfunction is identified in the setting of opioid pharmacotherapy, comprehensive evaluation is needed, and management is likely to be multifaceted, with consideration of:

- Mood, anxiety, and psychotic disorders and related psychotropic medication use including antipsychotics, "antidepressants," and sedative/hypnotics

- Other potentially treatable or reversible risk factors for sexual dysfunction including tobacco smoking, alcohol and other drug use, sleep apnea, and obesity (noting that exercise may be protective against sexual dysfunction)
- Issues related to poor self-esteem, including obesity and poor dentition
- Hormonal status, especially hypogonadism and hyperprolactinemia
- Partner status and relationship issues

Set within the larger issue of treatment planning, people may be prepared to tolerate side effects of pharmacotherapies if these are discussed, and their identification may provide a rational and structured context for goals in treatment.

Pharmacological strategies for hypoactive sexual desire include hormone replacement where there is hypogonadism. Centrally acting pro-dopaminergic and anti-serotonergic medications are the focus of current research (Stahl 2010). The centrally acting dopaminergic agent apomorphine is currently only available in Europe, and its use is limited by side effects especially nausea (Miner and Seftel 2007). One open-label uncontrolled study has reported successful use of the dopamine antagonist bromocriptine to treat sexual dysfunction in MMT (Shinderman and Maxwell 2000) on the thesis of likely hyperprolactinemia; however, prolactin levels were not measured, and hyperprolactinemia was uncommon in a cross-sectional study of men on MMT (Hallinan et al. 2008).

In both men and women with sexual dysfunction emergent with opioid, antidepressant or antipsychotic therapy, dose reduction, changing medications to alternatives with lower reported rates of sexual side effects, timing of medication in relation to planned sexual activity, and addition of phosphodiesterase type 5 inhibitors (PDE5-I) are all plausible strategies, though studies of these approaches are lacking (Schmidt et al. 2012; Rothschild 2000). As well as having favorable profiles for sexual side effects in monotherapy, the antidepressants bupropion, trazodone, and mirtazapine have shown benefit as add-on treatment to SSRIs. One open-label study has shown benefit of the serotonin antagonist and reuptake inhibitor trazodone for ED in men on MMT (Tatari et al. 2010).

Despite lack of a consistent dose relationship of sexual dysfunction to methadone dose in cross-sectional studies, it is likely that sexual dysfunction is dose related in any one individual and that dose reductions can help, provided this does not lead to relapse into other opioid use. With the same caveat, cross-sectional studies showing less prevalent sexual dysfunction in men on buprenorphine than methadone suggest possible benefit of switching medication.

109.2.7.1 Specific Issues for Women

Systemic testosterone may have a role for hypoactive sexual desire in surgically and naturally postmenopausal women (Davis et al. 2004; Nappi 2007). It is only approved for limited indications in a few European countries, although off-label use is common (Fooladi and Davis 2012). Typically transdermal formulations are used (Nappi 2007); oral administration of androgens should generally be avoided. Side effects including hirsutism, deepening of the voice (the latter can be irreversible), male pattern alopecia, and clitoromegaly can be troublesome, and these

should be discussed with patients when considering therapy. Longer-term risks include the possible increase in cardiovascular disease, as LDL cholesterol is elevated in laboratory tests in women on testosterone replacement. Another concern is the possibility of breast cancer with prolonged use: published studies are inadequate in duration to provide clear assurance, and most conclude that there is still a long-term possibility that this may be likely (Davis 2009). The use of testosterone in premenopausal has even fewer data to substantiate its use long term, and careful counseling must be used if this should be considered as treatment off-label.

Systemic estrogens with or without progestins can improve menopause-related symptoms, including reduced genital arousal and lack of vaginal lubrication. Topical estrogens may be preferred for equal efficacy and absence of systemic side effects and lower risk of breast cancer. Systemic HRT should be considered in postmenopausal women who use testosterone replacement, as the use of an unopposed sex steroid may add to long-term risks.

Evidence does not support benefit for estrogen treatment to increase sexual desire (Davis et al. 2004); indeed, estrogens might reduce desire. Estrogen-containing oral contraceptives were associated with lower circulating free androgens in premenopausal women with hypoactive sexual desire, partly due to increased SHBG (Warnock et al. 2006).

The PDE5 inhibitor sildenafil, in lower doses than are used in men, shows benefit for female sexual dysfunction related to multiple sclerosis, spinal cord injury, diabetes, and secondary to antidepressant use (Brown et al. 2009). Limited evidence exists for effectiveness of the melanocortin receptor agonist bremelanotide in women with arousal disorder (Safarinejad 2006).

109.2.7.2 Specific Issues for Men

PDE5-I are clearly effective for erectile dysfunction of a broad range of etiologies. They may be beneficial where erectile dysfunction is a side effect of opioid pharmacotherapy and where opioid dose reductions are likely to be counterproductive. They have advantages including on-demand effectiveness and absence of long-term side effects, but disadvantages including high cost (Stroberg et al. 2007). However, some men who have ED do not respond at all, or if so not longer term, to PDE5 inhibitors, and for some, these drugs are contraindicated. Currently available alternatives include intracavernosal injections.

In counseling, one should bear in mind that orgasmic dysfunction itself may contribute to erectile dysfunction, and loss of confidence and relationship stress can play a large role in perpetuating ED. Involvement of the partner in counseling may be helpful, and nondrug aids such as “cock rings” and vacuum devices are cheap and easily available or can be improvised.

The decision for androgen replacement in men should be informed by the possibility of placebo response and consideration and counseling regarding the possibility that initial benefit for sexual symptoms may not be sustained (Conway et al. 2000). Testosterone replacement for erectile dysfunction in hypogonadal males has shown benefit for erectile function, but not for sexual

desire or orgasm satisfaction (Chiang et al. 2009). In a cross-sectional study of men on MMT, testosterone accounted for only about 15 % of the variance in erectile function scores, while others have shown no association with testosterone levels, giving some perspective to the potential limits of androgen replacement for sexual dysfunction (Hallinan et al. 2008).

It is questionable whether androgen replacement should be considered where heavy alcohol use or uncontrolled opioid use continues. Concerns about excessive or otherwise inappropriate use of androgens can be minimized by prescribing transdermal formulations or limited supply and supervised administration of injected formulations.

109.2.7.3 Setting the Management of Sexual Dysfunction Within the Relationship

Relationship conflict can be a contributing factor in sexual dysfunction, which thus needs to be understood within the context of the sexual relationship. In management, it can be helpful to place the sexual problem within the context of the relationship rather than the individual. Schiavi (1990) suggests the need to consider the larger psychosocial context for sexual dysfunction in alcohol dependence in men.

At the same time, it must be recognized that people with AOD problems often have high levels of social dislocation, including disrupted or lacking intimate relationships. A high proportion of men on OST had no current regular sexual partner (Hallinan et al. 2008), whereby economic factors, low self-esteem, poor dentition, chronic viral infections, and many other factors may play a role. The capacity to elicit information about forms of sexual experience other than heterosexual intercourse, including "self-pleasure" (masturbation), is important in comprehensive assessment of sexual function and may pose special challenges in some cultures.

109.2.8 International Perspectives

Knowledge about the nexus of sexuality and AOD use is limited in many ways. Research has been greatest in Western societies, though there have been substantial contributions from East Asian countries and, in the case of opioid use, countries of the Middle East, especially Iran, albeit mainly for men. Indeed, there is generally much more information available about sexual dysfunctions for men than women, and in some countries, the sexual lives of women may be considered of low importance or not to be talked about. Discussion of sex altogether may be taboo in some cultures.

Instruments such as the International Index of Erectile Function (IIEF), while validated across a large number of countries and cultures, are designed for assessment of sexual function based on heterosexual intercourse within a partner relationship: estimates of prevalence of erectile dysfunction based on IIEF may be inflated by inclusion of men without partners. Numerous screening and research instruments can be used for both men and women, but few are widely validated, all having advantages and disadvantages: for clinicians, the challenge in any setting is to develop sensitive and culturally appropriate techniques of inquiry.

As with endocrine manifestations of addictive disorders, information is almost entirely lacking for some types of drug use common in certain cultures, such as khat, kava, coca chewing, or inhalant use. On the other hand, research from Western multicultural and multiethnic cultures, especially from the USA, does provide some reassurance about commonalities across ethnic groups.

109.3 Conclusion

Human sexuality is complex, and its disorders are often multifactorial, comprising a wide range of physiological, pathological, psychological, sociological, and cultural factors. Clinicians working in the field of AOD may find this very challenging, even daunting. However, the clinical benefits of addressing these issues, in a range of settings from reducing sexual risk behavior to improving quality of life of people receiving pharmacotherapies, can be substantial.

It is likely that better understanding of the relationship between sexuality and AOD use can enable more effective prevention, treatment, and harm reduction for AOD use, across all cultures, and therefore should be the focus of diverse future research endeavors.

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Substances of Abuse and Their Hormonal Effects

110

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Abstract

Substances of abuse can result in a multitude of systemic comorbidities. This is particularly true for metabolic and hormonal abnormalities which might complicate underlying medical conditions or may lead to new ones. This impact on the endocrine system depends on the type and length of exposure to substances of abuse and also the presence of any comorbid medical condition.

Sometimes their effects may be temporary and may mimic organic endocrine disorders such as Cushing's syndrome or hypothyroidism or hyperthyroidism. Abstinence may lead to reversal of these effects. Medical therapy may not be needed in these cases.

However, sometimes their effects may be either permanent, such as accelerated bone loss, or temporary but leading to severe symptoms from labile glycemic control or erectile dysfunction, necessitating treatment. The importance of the recognition of the effects of these substances of abuse on the endocrine system derives from the observation that abstinence from these substances helps reverse some of these effects.

In this review, we explore the various common substances of abuse and their impact on the endocrine system. Here we discuss the physiologic and laboratory abnormalities one might expect to find in the setting of substance abuse. We also discuss the endocrine disorders these individuals might be at a risk for, which may need either medical management of these primary endocrine effects or modification of the management of their comorbid medical conditions.

110.1 Introduction

The endocrine system is a complex interplay whereby some endocrine glands act directly in response to a stimulus, e.g., insulin in response to hyperglycemia, or indirectly through mediating hormones, such as releasing hormones from the hypothalamus. This chapter will review the effects of alcohol, amphetamines, tobacco, and cocaine on the endocrine system.

The hypothalamus is the coordinating center of the endocrine system. It consolidates signals derived from upper cortical inputs, autonomic function,

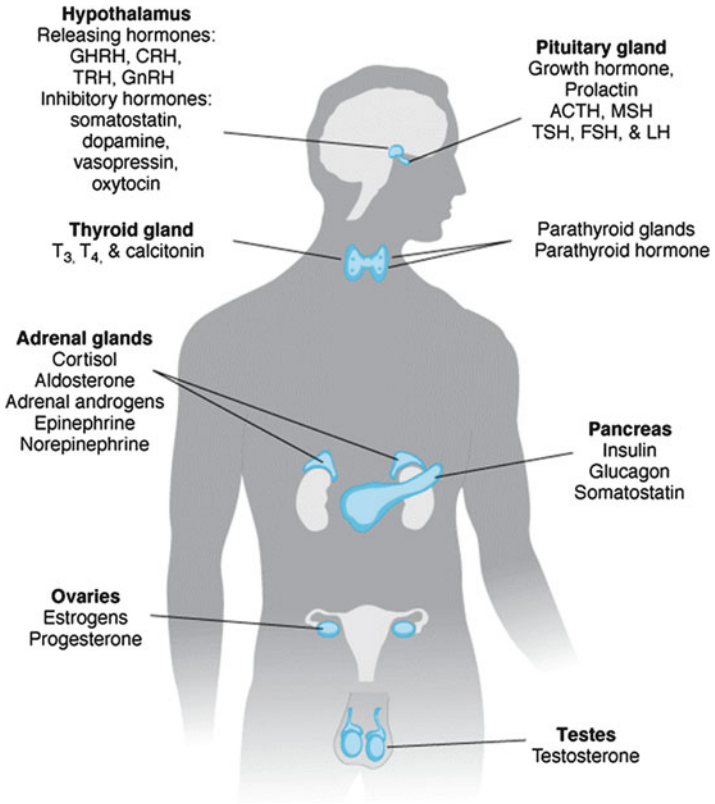

Fig. 110.1 Hormones secreted by the Endocrine Organs

environmental cues, and peripheral endocrine feedback. The hypothalamus receives input from virtually all other areas of the central nervous system and uses it to provide input to the pituitary. The hypothalamus controls output of the anterior pituitary by means of hormones, and it controls the output of the posterior pituitary or neurohypophysis by direct stimulation or inhibition. The interaction between the hypothalamus, the pituitary gland, and the other endocrine glands is a feedback control system (Emanuele and Emanuele 1997). Figure 110.1 is an overview of the feedback loops illustrating the key role of pituitary function on the thyroid, adrenal, and gonadal organs.

Drugs of abuse often disrupt the hypothalamic-pituitary-endocrine axis, causing the endocrine glands to either over- or underproduce. Disruptions of the endocrine system occur in various ways. Some chemicals mimic a natural hormone, fooling the body into overresponding to the stimulus or responding at inappropriate times. Others will directly affect various endocrine glands leading to overproduction or underproduction of hormones.

The effects of different drugs of abuse on the endocrine system are multiple and complex. These substances impair both the functions of the glands that release

hormones and the tissues to which they are being sent. The type, length, and pattern of exposure; level of intoxication and withdrawal; and coexisting medical problems often predict the degree of endocrine disruption. In this chapter, we summarize the effects of both acute and chronic exposures of different drugs of abuse, on the endocrine system addressing basic and clinical evidences performed on animal and human models.

110.2 Alcohol

The effects of alcohol on endocrine function are dependent on the type, length, and pattern of alcohol exposure; level of intoxication; and coexisting medical problems. Malnutrition and liver dysfunction must also be considered when assessing the impact of alcohol on hormonal status.

110.2.1 Effects of Alcohol on the Adrenal Gland

Alcohol causes an activation of the hypothalamic-pituitary-adrenal (HPA) axis resembling Cushing's syndrome, a disease stemming from an excess of cortisol, called alcohol-induced pseudo-Cushing's syndrome (Emanuele and Emanuele 1997). This is clinically similar and sometimes indistinguishable from true Cushing's syndrome. The condition is characterized by abdominal obesity and stria, with evidence of hypercortisolism on a 24 h urine collection. Cortisol levels are particularly higher during an episode of acute intoxication and begin to decline during withdrawal, returning to baseline levels appropriate in a normal person after complete abstinence (Kutscher et al. 2002). The features of this pseudo-Cushing's syndrome would completely disappear after at least 2–4 months of abstinence (Kutscher et al. 2002). There is no need to treat this pseudo-Cushing's syndrome.

Besides the physical stigmata of Cushing's, disruption of the HPA axis by chronic alcohol exposure can result in medical consequences including abdominal obesity, hyperinsulinism, glucose intolerance, and depression of the immune system. Chronic hypercortisolemia itself has been known to suppress the immune system. Both alcohol intoxication and withdrawal may potentially alter immune function via other neuroendocrine mechanisms such as disrupted sympathetic nervous system and elevations of other pituitary hormones producing abnormalities in the function and distribution of immune cells (Kutscher et al. 2002). While individuals are predisposed to infections due to hypercortisolemia during the intoxication phase, the basal cortisol level returns to near normal in the first week of abstinence. However, the responses of cortisol and ACTH are blunted to corticotropin-releasing hormone (CRH) within the first 2 weeks after abstinence from alcohol (Adinoff et al. 1990). This might contribute to a depressed response to stresses, such as infections during this phase.

110.2.2 Effects of Alcohol on Thyroid Function

Many studies have been done where different effects were seen on the thyroid hormone levels in alcoholics. In a few studies it was shown that chronic alcoholism was associated with lower thyroid gland volume and T3 and T4 secretion, presenting as a euthyroid sick syndrome (ESS) in the setting of normal TSH. Alcohol disrupts thyroid function at several steps starting from damage to the deiodinases used in the thyroid hormone synthetic and conversion pathways to an increase in the TBG seen in patients with alcoholic liver disease and fibrosis and reduction in thyroid volumes seen in patients with cirrhosis (Hermann et al. 1997). Damage to the deiodinases has been implicated in intracellular hyperthyroidism resulting in symptoms of withdrawal like hallucinations, tremors, anxiety, palpitations, and diaphoresis. However, while this is happening at an intracellular level, the TSH response to TRH becomes blunted in subjects going through alcohol withdrawal. This mimics the signs and symptoms of peripheral hypothyroidism.

Interestingly, patients with chronic alcohol exposure have been found to have a lower incidence of solitary thyroid nodules and multinodular goiter (Knudsen et al. 2001).

110.2.3 Effects of Alcohol on Gonadal Hormones

110.2.3.1 In Men

Chronic alcohol abuse produces sexual dysfunction and impairs sperm production in both animal models and humans (Emanuele and Emanuele 2001). It was observed that alcohol not only reduced synthesis of testosterone resulting in low testosterone levels but also impaired the secretion of LH in response to low testosterone levels, by directly causing Leydig cell dysfunction. Another mechanism that results in male hypogonadism includes its disruption of the inhibitory effect of dopamine on prolactin. This results in an increased prolactin secretion which suppresses gonadal testosterone synthesis leading to impotence and infertility (Emanuele and Emanuele 1997, 2001).

The consequences of low levels of testosterone in adult men have resulted in a variety of health issues including osteoporosis, decreased muscle and prostate function, anemia, altered immune function, and decreased reproductive ability (Klein and Duwall 1994; Jackson and Klerekoper 1990; Azad et al. 1991). Each of these conditions can cause significant health problems. Younger men who have had low testosterone in adolescence due to alcohol abuse are more prone to these health effects than older men (Emanuele and Emanuele 2001).

The obvious treatment of alcohol-induced male hypogonadism might be cessation of alcohol. Although one can assume that the testosterone levels will return to normal, there are no studies that have proven this. Similarly, although not directly studied, testosterone replacement therapy can be offered to men and may help with improved muscle strength and libido. Dopamine agonists like bromocriptine may not be effective to treat alcohol-induced hyperprolactinemia as ethanol itself can

reduce bromocriptine's ability to reduce prolactin secretion (Oomizu et al. 2003). Alcohol can also cause neuropathy, which in turn can also lead to impotence (Emanuele et al. 1998). Thus, multifactorial causation of sexual dysfunction and infertility should be kept in mind in alcoholic men.

110.2.3.2 In Women

Moderate drinkers, i.e., women who have more than three drinks per day, had significant menstrual problems ranging from anovulation and delayed ovulation to infertility and an increased frequency of spontaneous abortions (Mendelson and Mello 1998). Acute alcohol consumption was associated with an increase in estrogen levels (Emanuele and Emanuele 1997), which suppresses FSH (Mello et al. 1993) leading to impaired folliculogenesis and impaired function of the corpus luteum resulting in infertility from anovulation. Alcohol also directly suppresses progesterone secretion from the corpus luteum, thus putting a woman at risk of spontaneous abortions. Also, alcohol-induced hyperprolactinemia can contribute to menstrual irregularities and amenorrhea (Emanuele and Emanuele 1997). Prolactin should be measured in all evaluations of the hypothalamic-pituitary-gonadal (HPG) axis.

The consequences of alcohol on the fetus are well known, causing fetal alcohol syndrome. Yet, there is a growing understanding that women trying to conceive should be counseled to stop drinking any alcohol so as to maximize their pregnancy capability.

110.2.4 Effects of Alcohol on the Pancreas

Chronic alcohol consumption by itself can lead to chronic pancreatitis and new onset diabetes from insulin deficiency. However, in patients with preexisting diabetes, alcohol affects glycemic control in various ways, depending on whether the alcohol ingestion is acute or chronic and whether it is consumed in the fed or fasted state (Emanuele and Emanuele 1997).

110.2.4.1 Effects on Blood Glucose While in the Fed State

While in the fed state, occasional alcohol ingestion (acute) with meals does not produce clinically significant effects on blood glucose in diabetic males or females (Emanuele et al. 1998). However, long-term consumption of alcohol (chronic) in well-nourished diabetics can lead to clinically significant elevated fasting blood glucose, as well as high hemoglobin A1c levels. The mechanism involved here could be due to increased insulin resistance or reduced insulin secretion or both (Emanuele et al. 1998). Also, chronic alcoholics may show noncompliance with their dietary and medication regimens leading to poor control of blood sugars.

110.2.4.2 Effects on Blood Glucose in the Fasting State

Diabetics consuming alcohol in the fasting state can experience serious life-threatening complications of hypoglycemia induced by alcohol. This occurs due to impaired glycogenolysis due to rapid depletion of stores in the liver while fasting

and shutdown of gluconeogenesis in the liver by alcohol metabolism. Unlike nonalcoholic diabetics, the individual with both diabetes and alcoholism often has hypoglycemic unawareness and does not sense the classic symptoms of hypoglycemia, i.e., shakiness, sweating, restlessness, nervousness, and palpitations. This can lead to delayed recognition of hypoglycemia, resulting in delayed treatment and even death.

In type 1 diabetics, consuming alcohol in a fasting state can have grave consequences as they also have a delayed recovery from hypoglycemia, due to alcohol-mediated impairment of counter-regulatory responses to hypoglycemia (Adinoff et al. 1990). As stated above, impaired cortisol response during the withdrawal phase can also aggravate any hypoglycemia.

Heavy drinkers are also at risk for alcoholic ketoacidosis in the fasting state, from depletion of glycogen stores and low levels of insulin, in addition to being at risk of hypoglycemia. Chronic heavy drinkers are also at risk of alcoholic pancreatitis from hypertriglyceridemia which can also contribute to the risk of pancreatitis. Chronic pancreatitis can further cause progression of diabetes in type 2 diabetics, from insulin-resistant to insulin-deficient diabetes. Finally, chronic alcohol consumption can impair liver function, thus creating contraindications to the use of metformin and thiazolidinediones in type 2 diabetics.

110.2.5 Effects of Alcohol on Bone Metabolism

Chronic alcohol consumption can lead to impaired bone growth and repair leading to reduced bone density and fractures (Sampson 1998). This occurs at various levels; alcohol leads to malabsorption of calcium from the gastrointestinal tract resulting in low calcium levels in the blood, which in turn increases parathyroid hormone (PTH) levels. This leads to bone resorption and demineralization and poor bone density (Emanuele et al. 1998). Also, alcohol through its blunting effect on sex hormones has a direct suppressive effect on the osteoblasts, impairing bone remodeling and repair and further increasing the risk of fractures (Emanuele and Emanuele 2001; Emanuele et al. 1998; Sampson 1998). The common scenario includes low serum calcium, high PTH levels, and low phosphorus levels. Low phosphorus levels brought about by high PTH promoting excretion of phosphate in the urine can further cause muscle weakness restricting the mobility of these patients (Sampson 1998).

110.2.5.1 Summary of the Alcohol Effects on the Endocrine System

Alcohol consumption, both acute and chronic, has both direct and indirect effects on nearly every hormonal system. Alcoholism is highly likely to result in a pseudo-Cushing's syndrome, suppression of gonadal hormones, abnormal thyroid function tests, hyperglycemia and blunted responses to hypoglycemia, and a predisposition to metabolic bone disease. The patient who suffers from acute or chronic alcohol use should be thoroughly evaluated for possible hormonal dysregulation and aggressively treated.

110.3 Amphetamine/Methamphetamine

110.3.1 Effects of Amphetamines on Thyroid Function

The signs and symptoms of amphetamine abuse are similar to those of thyrotoxicosis and include restlessness, tremor, hyperactive reflexes, irritability, weakness, palpitations, cardiac arrhythmias, diarrhea, excessive sweating, and increase in basal metabolic rate. In fact, some have suggested that these signs and symptoms are in fact due to hyperthyroxinemia. Amphetamine-treated animals showed increase in TSH 30 min after treatment and elevation of T4 120 and 180 min after treatment, and T3 was not significantly altered by treatment, suggesting that the amphetamines stimulate thyroid hormone secretion through the hypothalamic or pituitary level (Morley et al. 2008).

110.3.2 Effects of Amphetamines on the Adrenal

Amphetamines increase serum corticosterone concentration after acute administration; however, chronic or repeated amphetamine injections reduce normal elevation of plasma corticosterone (Budziszewska et al. 1996), although in other studies, amphetamine has shown no consistent change in plasma cortisol (Feinberg et al. 1981).

110.3.3 Effects of Amphetamines on the Gonads

The effect of amphetamines on sexual function is variable. While some reported amphetamine users experienced decreased sexual drive, other amphetamine dependents have described an increased sexual libido and intense orgasm. There are also some noteworthy findings that reveal a low dose of amphetamine increases a male's sexual libido and that a high dose and frequent use of amphetamine can trigger several sexual dysfunctions such as decreased sexual drive, prolonged erection, delayed ejaculation, prolonged sexual intercourse, and multiple orgasms (Abel 1985). In an animal study, methamphetamine has showed a dose-dependent decreased percentage of normal sperm morphology and sperm count and induced apoptotic cell activities within the seminiferous tubules (Nudmamud-Thanoi and Thanoi 2011).

110.3.4 Effects of Amphetamines on Growth Hormone

Amphetamine use is correlated with increments in growth hormone and elevation, suggesting excitatory control by dopaminergic system (Brown et al. 1978).

110.3.4.1 Summary of the Effects of Amphetamines on the Endocrine System

There are very mild effects of amphetamine use on the endocrine axis, and most of these are variable. Because of the overlap between symptoms of amphetamine overdose and hyperthyroidism, thyroid function tests should be measured in this population.

110.4 Marijuana/Cannabis

Marijuana is one of the most widely used illicit substances, and there is growing interest in the pharmacological strategies and therapeutic possibilities of this drug, as it becomes legalized in more US states. While known to modulate neuroendocrine function, the precise acute and chronic dose-related clinical consequences of marijuana and its active component delta-9-tetrahydrocannabinol (THC) in humans are still unclear (Ranganathan et al. 2009; Ashton 2001; Brown and Dobs 2002).

110.4.1 Acute vs. Chronic Effects

Animal models have demonstrated that cannabinoid administration acutely alters multiple hormonal systems, including the suppression of the gonadal steroids, growth hormone, prolactin, and thyroid hormone and the activation of the HPA axis. These effects are mediated by binding to the endogenous cannabinoid receptor in or near the hypothalamus. Many of these acute effects, however, are transient as tolerance likely develops (Brown and Dobs 2002).

The long-term consequences of marijuana use in humans on the endocrine systems remain unclear. Chronic cannabis use appears to carry reproductive risks, both to the mother during pregnancy and childbirth and to the fetus and neonate, although these areas need further study (Brown and Dobs 2002). The full extent of long-term health risks of chronic cannabis use (if today's young smokers continue the habit) may require a latent period of 10–20 years to be revealed (Ashton 2001).

110.4.2 Effects of Marijuana on Thyroid Function

In animals, THC decreases circulating TSH, T3, and T4 levels (Hillard et al. 1984); reduces iodine accumulation (Miras 1965); and decreases the release of radioactive iodine from the thyroid (Lomax 1970). These effects are reversed by administration of exogenous TSH, suggesting a hypothalamic site of action. With chronic administration of THC, the thyroid depressant effect of cannabinoids is lost, which again may indicate the development of tolerance. Data are scarce regarding the effect of cannabinoids on thyroid function in humans (Brown and Dobs 2002).

110.4.3 Effects of Marijuana on the Adrenals

THC raises plasma cortisol levels in a dose-dependent manner, but frequent users show blunted increases, likely due to tolerance, relative to healthy controls (Ranganathan et al. 2009).

110.4.4 Effects of Marijuana on the Gonads

Exposure to THC, the main psychoactive constituent of marijuana, impairs human reproductive potential by disrupting the menstrual cycle, suppressing oogenesis, impairing embryo implantation and development (Bari et al. 2011), and reducing prolactin levels and inhibiting milk production and maintenance of lactation (Bonnin et al. 1993; Ranganathan et al. 2009; Brown and Dobs 2002) in women and by increasing ejaculation problems, reducing sperm count and motility, generating loss of libido and impotence (Bari et al. 2011), and gynecomastia (Harmon and Aliapoulios 1972; Brown and Dobs 2002) in men.

110.4.5 Effects of Marijuana on the Neuroendocrine Regulation of Feeding

The endocannabinoid system has a role on brain reward pathways, enhancing the hedonic value of food. Cannabinoids stimulate appetite and food intake, likely through the activation of central cannabinoid (CB1) receptors in hypothalamic feeding centers (Brown and Dobs 2002).

110.4.5.1 Summary of Cannabinoid Effects on the Endocrine System

Cannabinoids can affect various neuromodulatory systems in both the acute and the chronic exposures. While acutely its effects are mainly seen on the adrenals and the gonads, data have not focused on long-term use, which will likely be more commonly observed as marijuana becomes legal.

110.5 Tobacco/Smoking

Smoking has known to be associated with many cardiovascular diseases, as well as cancers. Smoking however also affects the endocrine system affecting almost every part of it.

110.5.1 Effects of Cigarettes on the Adrenals

Nicotine is a strong activator of the HPA axis. Smoking as little as two cigarettes consistently activates the HPA axis of habitual smokers. However, while being

a habitual smoker only induces small changes of basal HPA axis activity, smoking induces an attenuated responsiveness of the HPA axis to psychological stress (Rohleder and Kirschbaum 2006). The ACTH and cortisol levels were higher after smoking cigarettes containing higher level of nicotine than controls (Mendelson et al. 2008). This was also shown to have some role in developing an addiction to nicotine especially when the user is under any kind of psychological stress.

Smoking also increased DHEA levels by stimulating the HPA axis. Increases in DHEA levels may contribute to the mood-elevating effects reported after cigarette smoking, as well as to the alleviation of anxiety and depression (Picciotto et al. 2002).

However, similar increases in ACTH, cortisol, and DHEA levels were not seen after the use of low-dose nicotine cigarettes. Low levels of cortisol and DHEA have also been seen in early abstinence and nicotine withdrawal and may be associated with a relapse. Studies have also shown that nicotine replacement may not increase cortisol levels similar to cigarettes, thus also contributing to a relapse from smoking cessation (Mello 2010).

110.5.2 Effects of Cigarettes on the Gonads

Approximately 30 % of women of reproductive age and 35 % of men of reproductive age in the United States smoke cigarettes. Available data indicate that up to 13 % of infertility may be attributable to cigarette smoking (Pfeifer et al. 2012).

There is good evidence that semen parameters and results of sperm function tests are 22 % poorer in smokers than in nonsmokers and the effects are dose dependent (Pfeifer et al. 2012). In men, higher FSH and LH and lower testosterone levels were seen with increased smoking in a study (Mitra et al. 2012). Nicotine, one of the toxic components in cigarette smoke, had been reported to inhibit androgen biosynthesis and Leydig cell growth (Bergmann et al. 1994; Funabashi et al. 2005) which might be responsible for the observed decline in testosterone among the heavy smokers. A high FSH level is usually diagnostic of primary testicular failure, a condition in which the seminiferous tubules in the testes do not produce sperm normally, because they are damaged. Reduced testosterone levels and mutation in the androgen receptor gene, due to exposure to nicotine, may impact the feedback to LH, resulting in elevated LH levels.

In women, smoking appears to accelerate the loss of reproductive function and may advance the time of menopause by 1–4 years. There is evidence that smoking is associated with increased risks of spontaneous abortion and ectopic pregnancy. Gamete mutagenesis is one possible mechanism whereby smoking may adversely affect fecundity and reproductive performance in the offspring. There is good evidence that smokers require nearly twice the number of IVF attempts to conceive as nonsmokers (Pfeifer et al. 2012).

The adverse effects of sidestream and passive smoking are now established, and there is good evidence that nonsmokers with excessive exposure to tobacco smoke may have similar reproductive problems as smokers.

110.5.3 Effects of Smoking on Thyroid Function

Current smoking lowers serum TSH (Mehran et al. 2012) by about 0.3 mU/l (Weirsinga 2013). The effect is dose dependent and disappears slowly after cessation of smoking. The effect is not associated with ambient iodine intake and is accompanied by a slight rise of serum FT3 and FT4. This might be mediated by activation of the sympathetic nervous system stimulating the production and release of thyroid hormone.

Interestingly, smoking reduces the risk of Hashimoto's thyroiditis (diminishing the occurrence of TPOAb and TgAb and autoimmune hypothyroidism) by about 40 %. This effect might be related to activation of nicotine receptors on immune cells.

Current smoking increases the risk of Graves' hyperthyroidism about twofold and of Graves' ophthalmopathy about threefold (Weirsinga 2013). Current smoking is associated with a higher recurrence rate of Graves' hyperthyroidism, a higher risk on Graves' ophthalmopathy after 131I therapy, and a less favorable outcome of Graves' ophthalmopathy treatment with steroids or retrobulbar irradiation. Cessation of smoking reduces the risk of Graves' disease and ophthalmopathy (Vestergaard 2002).

Current smoking carries a risk for nontoxic goiter and multinodularity. It also increases thyroid size by about 3 ml in men and 1 ml in women. Thiocyanate in cigarette smoke is a competitive inhibitor of thyroidal iodine uptake and is goitrogenic. This is more commonly seen in iodine-deficient areas (Weirsinga 2013).

Current smoking reduces the risk of differentiated thyroid carcinoma by about 40 %. The effect is more pronounced for papillary than follicular cancers and the effect may disappear after cessation of smoking. The effect might be related to some extent to lower TSH and lower body mass index in current smokers (Weirsinga 2013). Further studies are required to analyze the contrasting effects of smoking on the thyroid.

110.5.4 Effects of Cigarettes on the Pancreas

Smoking reduces the risk of developing type 1 diabetes mellitus because of a possible inhibitory effect on autoimmune processes (Rasouli et al. 2013). However, it was associated with a higher risk of developing type 2 diabetes mellitus as well as worsening control of diabetes due to increasing insulin resistance. This effect was seen more in obese individuals as compared to lean men or those with lower BMI <25 (Rasouli et al. 2013).

Heavy smokers had larger waist circumference and abdominal obesity, which plays a role in worsening insulin resistance (Yun et al. 2012). However, the same study also showed that the overall BMI was lowest in current smokers, intermediate in never smokers, and higher in former smokers, reflecting a possible effect of nicotine on appetite suppression and increased metabolic rate.

Thus, while smokers weighed less than the nonsmokers, the fat distribution was more central, contributing not only to impaired insulin resistance but also puts a person at risk for dyslipidemias, hypertension, and cardiovascular disease.

110.5.5 Effects of Cigarettes on Bone Metabolism

Cigarette smoking affects bone health by reducing the bone mineral density, thus increasing the risk for osteoporosis. This has been observed in postmenopausal and aging-related bone loss (Lee et al. 2013). Cigarette smoking leads to increased fracture rates of the hip, spine, and distal radius and other osteoporosis-associated fractures. The mechanism for this is unclear, but likely related to nicotine-induced vasoconstriction, causing tissue hypoxia and increased bone turnover activity (Lee et al. 2013) This not only increases the risk of sustaining a fracture but also impairs bone healing and the risk of osteonecrosis. Studies have shown that smokers are at higher risk for nonunion and delayed union of fractures and have increased incidence of osteomyelitis than nonsmokers (Castillo et al. 2005).

110.5.5.1 Summary of Smoking Effects on the Endocrine System

Smoking is one of the strongest risk factors for cardiovascular disease. Its effects on the endocrine system, particularly the reproductive axis, are not as well known. The effect of cigarettes on subfertility in the mother and male fetus can have profound effects on the next generation.

110.6 Cocaine

Cocaine is a powerfully addictive stimulant drug made from the leaves of the coca plant native to South America. It produces short-term euphoria, energy, and talkativeness in addition to potentially dangerous physical effects like raising heart rate and blood pressure. Cocaine abuse and dependence continues to be one of the nation's most serious drug abuse problems, and the associated social and economic costs include a number of adverse effects on health.

Drugs like cocaine affect mood, stress, cognition, and energy; these drugs may lead to or potentiate depressive symptomatology and reduced quality of life.

110.6.1 Effects of Cocaine on the HPA Axis

Cocaine interacts with many neurohormonal systems in the brain and has both direct and indirect effects on the anterior pituitary, and adrenal hormones. Both acute and chronic exposures to cocaine have been shown to result in increased levels of ACTH and thus cortisol, resulting in associated effects from cortisol excess such as impaired glucose tolerance and insulin resistance, raised BP, and immune suppression (Mello and Mendelson 1997). Cortisol excess and the use of

cocaine by itself can affect body composition negatively impacting cardiovascular health (Brown et al. 2006).

Cocaine also has a dopamine agonist action similar to a MAO inhibitor and has mood-elevating effects in cocaine abusers. In addition to that, prolactin levels are found to be decreased in this population as dopamine has an inhibitory effect on prolactin secretion (Mello and Mendelson 1997). Its dopamine agonistic actions also contribute to elevated heart rate and blood pressures seen in cocaine abusers.

110.6.2 Effects of Cocaine on the Gonads

Cocaine administration leads to reduced circulating testosterone levels, in men, likely through reduced LH release (Mendelson et al. 2001). The resulting male hypogonadism can lead to multiple metabolic complications, including decreased sexual function, reduced lean body mass and bone mass, and adverse cardiovascular health (Brown et al. 2006). Alterations in LH secretion were also associated with dysfunctional mood in both men and women. In women, cocaine use was also reported to be associated with reduced secretion of LH and disruption of menstrual cycle (Mello and Mendelson 1997).

110.6.3 Effects of Cocaine on Thyroid Function

Thyroid hormone levels, both T3 and free T4, have been reported to be normal in patients abusing cocaine (Burke and Dhopesh 1993). However, there has been a case report of hyperthyroidism in a cocaine-abusing patient, but no definite causal association has been proven yet.

In one such study, TSH response was found to be blunted to TRH administration in a cocaine-using population, which might present a hyperthyroid-like picture. TSH was found to be more responsive to TRH during a period of abstinence from cocaine, in the same study (Vescovi and Pezzarossa 1999).

110.6.4 Effects of Cocaine on Growth Hormone

TRH was found to stimulate GH secretion in patients with a history of cocaine dependence, during a period of abstinence. This was seen in the same study which studied the response of TSH to TRH (Vescovi and Pezzarossa 1999).

110.6.5 Effects of Cocaine on the Pancreas

Cocaine abuse makes patients with type 1 diabetes mellitus at risk for diabetic ketoacidosis (DKA) (Ng et al. 2004). It may also be an independent risk factor for development of recurrent DKA in type 2 diabetics, either directly or through

Table 110.1 Substance abuse and associated endocrine abnormalities

Drug	Adrenal	Thyroid	Gonads	Pancreas (diabetes mellitus)	Bone
Alcohol	Cortisol ↑	Euthyroid sick syndrome: TSH remains normal; T3 and T4 are lowered	In men: ↓LH and testosterone Sperm count ↓ Impotence Infertility	In the fasting state: Hypoglycemia Impaired counter-regulatory response to hypoglycemia Alcoholic ketoacidosis	Calcium malabsorption, ↑PTH ↓Phosphorus ↓Bone density ↑Risk of fractures Muscle weakness
			In women: Anovulation Menstrual irregularities Infertility Spontaneous abortions	In the fed state: Fasting blood sugars↑ Hemoglobin A1C↑	
Amphetamine	Acute: ↑cortisol Chronic: ↓cortisol	Hyperthyroxinemia: TSH, T4, T3 same	Variable, sexual desire orgasm		
Marijuana	Cortisol ↑	TSH, T3, and T4 ↓	In men: Ejaculation problem Sperm count and motility ↓ ↓Libido Impotence Gynecomastia		
			In women: Disrupt menses		

(*continued*)

Table 110.1 (continued)

Drug	Adrenal	Thyroid	Gonads	Pancreas (diabetes mellitus)	Bone
			Oogenesis↓ Impairs embryo implantation and development ↓Prolactin		
			↓Milk production and maintenance of lactation		
Tobacco	Cortisol↑	TSH ↑FreeT4, ↑FreeT3	In men: Damage to the seminiferous tubules Poor sperm quality Leydig cell dysfunction – >low testosterone Androgen receptor mutation ↑LH ↑ FSH	↓Risk of autoimmune diabetes	↓Bone mineral density
	DHEA ↑: elevates mood and relieves anxiety	↑Risk of Graves' hyperthyroidism and ophthalmopathy		↑Risk of developing type 2 diabetes	Accelerated bone loss
		↓Risk of Hashimoto's thyroiditis		Worsening insulin resistance and glycemic control in type 2 diabetics	Osteoporosis
		↑Risk of nontoxic thyroid goiter and multinodularity	In women: Gamete mutagenesis Spontaneous abortions Ectopic pregnancy		↑Fragility fractures
		↓Risk of differentiated especially papillary carcinoma			Impaired bone healing Osteonecrosis
Cocaine	Cortisol ↑	Both T3 and T4 usually tend to be normal	In men: ↓LH and Testosterone	Stimulates secretion of counter-regulatory catecholamines increasing risk of diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome	Reduced bone mass due to its effects on testosterone
	In pituitary: Dopamine agonistic effects similar to MAO inhibitors – elevates mood	TSH less responsive to TRH	Sexual dysfunction In women: ↓LH Menstrual irregularities Mood disruptions in both men and women		

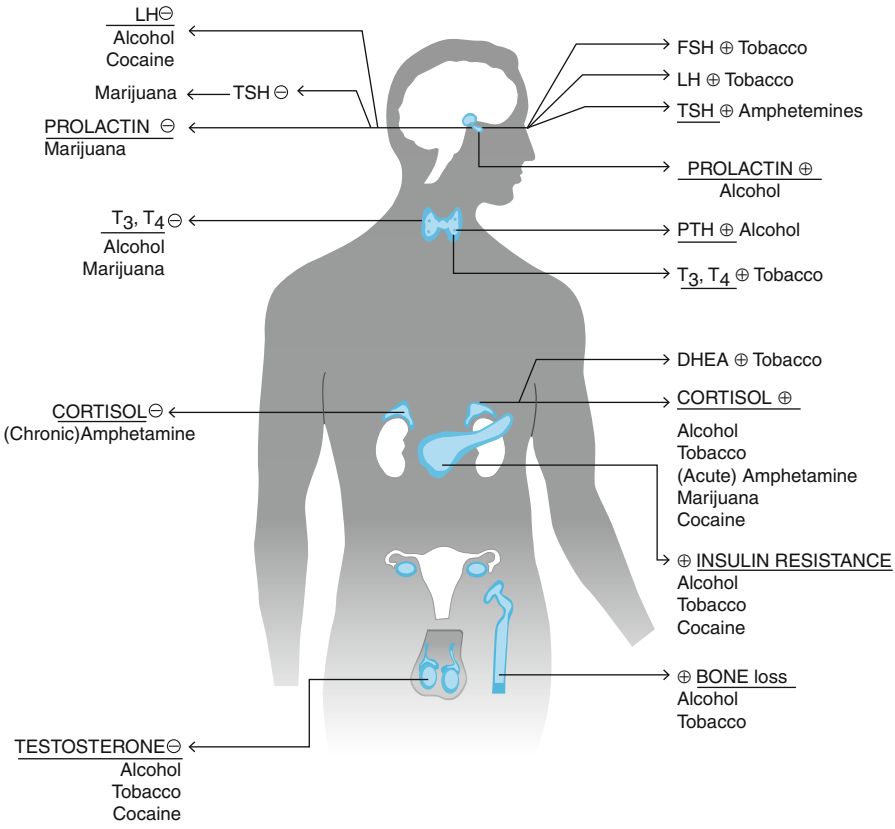

Fig. 110.2 Schematic Summary of the Hormonal Effects of the Substances of Abuse

noncompliance with glucose-lowering medications (Nyenwe et al. 2007). In fact, hyperosmolar hyperglycemic nonketotic state was the initial presentation of new onset diabetes mellitus (Abraham and Khardori 1999). These complications may be seen mainly due to the stimulatory effect of cocaine on counter-regulatory hormones by stimulating release of catecholamines such as epinephrine from the adrenal medulla.

110.6.5.1 Summary of Cocaine Effects on the Endocrine System

Cocaine has direct and indirect effects on several neuromodulatory systems. It leads to multiple systemic effects by affecting glycemic control, the adrenals, and the gonads.

110.7 Conclusion

Substances of abuse put people at risk for numerous endocrine abnormalities and metabolic complications. These abnormalities in themselves can have long-term

sequelae affecting the addict's health. A good history and physical exam, including a detailed history review of the endocrine axes, will help to identify possible endocrine disorders. Endocrine abnormalities are common in the population and can be present as an underlying comorbidity, or drugs of abuse can cause or aggravate underlying endocrine problems. Health-care providers need to know what possible defects may arise in the setting of polysubstance abuse to be able to treat and thus prevent long-term metabolic complications (Table 110.1, Fig. 110.2).

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Patients with Substance Use Disorders and Addiction: Perioperative Issues

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Tim Neumann and Claudia Spies

Contents

The list of references was limited to 70 citations. We acknowledge a multitude of additional contributions that are not mentioned here. This paper reflects also some of the work of many other colleagues in this understudied field.

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Abstract

Patients with substance use disorders are seen frequently in perioperative settings. It has been estimated that every third patient undergoing surgery is smoking; every fifth patient has alcohol use disorders such as hazardous use, abuse, harmful consumption, or dependence; every tenth patient is alcohol dependent; and every twelfth patient is consuming drugs regularly. Many patients use more than one substance regularly. Substance use disorders do vary in severity. Substance use is associated with significant somatic and psychiatric morbidity. Perioperative complications occur more often, even if underlying pathophysiological changes are subclinical. As an example, bleeding time can be prolonged, infection rate can be increased, cardiopulmonary complications can occur, or wound healing can be impaired even without clinical signs of, e.g., manifest liver cirrhosis and cardiovascular or lung disease. Patients with substance use disorders can safely undergo procedures under anesthesia. There are a variety of evidence-based treatment options to treat or prevent complications related to substance use. By secondary or tertiary preventive measures in a multimodal interdisciplinary concept, the increased risk can be significantly reduced. Elements are systematic screening, including the use of questionnaires and biomarkers, systematic diagnostic evaluation, brief interventions, tailored advice and information, patient-centered communication, tailored anesthesia, detoxification, abstinence, rehabilitation, psychosocial therapy, stepped care, monitoring of withdrawal symptoms, and prevention of withdrawal symptoms with pharmacological substitution therapy, monitoring and prevention of complications, goal-oriented therapy, symptom control, stress reduction, prevention of secondary injury, complex interdisciplinary treatment strategies, and teaching and training of the staff.

111.1 Introduction

Patients with substance use disorders (SUD) are seen frequently in perioperative settings. It has been estimated that every third patient undergoing surgery is smoking; every fifth patient has an alcohol use disorders such as hazardous use, abuse, harmful consumption, or dependence; every tenth patient is alcohol dependent; and every twelfth patient is consuming drugs regularly. These patients require medical care more often and more extensively. Substance use is associated with somatic and psychiatric morbidity. Perioperative complications occur more often, even if underlying pathophysiological changes are subclinical. As an example, bleeding time can be prolonged, infection rate can be increased, cardiopulmonary complication can occur, or wound healing can be impaired even without clinical signs of, e.g., manifest liver cirrhosis and cardiovascular or lung disease (Spies et al. 2001b; Tønnesen et al. 2009; Kork et al. 2010).

The term "substance use disorder" describes a continuum ranging from risky use over heavy use, hazardous use, abuse, harmful consumption to dependence. As we observe often similar morbidity among risky users as in dependent patients, it

seems to be more appropriate from the clinical point of view to describe relevant perioperative issues in all patients with substance use disorders without focusing on patients with physical dependence, with compulsive drug-seeking behavior, and with tolerance or with withdrawal. For didactic reasons alcohol, nicotine, and drug use disorders are described in distinct chapters as usual. However, many patients use more than one substance regularly.

In contrast to many other medical conditions, patients with SUD do often not get adequate treatment in the perioperative context. This has been related to underreporting and underasking. A variety of factors have been described: stigma or fear of stigma, lack of time and resources, lack of training, projections, and many (false) myths about the origin of these disorders. Early detection of SUD and their associated risk is essential to reduce complications, but an SUD is often suspected after complications occurred (Spies et al. 2001b; Runge et al. 2001; Tønnesen et al. 2009; Kork et al. 2010). Intoxication or acute delirium can interfere with the clinical presentation of other severe conditions (e.g., traumatic brain injury and alcohol intoxication, delirium, and thiamine deficiency). Therefore, the evaluation of all patients with SUD requires well-directed and proactive diagnostic approaches (Neumann and Spies 2003).

Many pathophysiological changes and organ dysfunctions in relation to substance use are potentially reversible by abstinence. The extent of recovery depends on the progression of the disease (Tønnesen et al. 2009).

The patient-doctor interaction is somehow different from what is seen in addiction centers. Patients undergoing surgery are usually expecting to receive the best surgery with a minimal risk, but are not actually seeking treatment for SUD. A comprehensive preoperative risk assessment is standard and substance use is a risk factor. Risks and risk-reducing options are discussed in order to reach informed consent. Most patients found alcohol intervention relevant in relation to surgery. Therefore, all steps should be explained to patients in their own language. Patient preferences should be explored. A working alliance should be established. The FRAMES concept (feedback, responsibility, advice, menu of behavioral changes, empathy, self-efficacy) summarizes useful elements of the communication. Patients with relevant psychiatric (co)morbidity should be seen by a psychiatrist (Spies et al. 2006b; Kork et al. 2010; Lau et al. 2011; Pedersen et al. 2011).

When a SUD is suspected, a brief intervention should be offered. Interventions like motivational interviewing are directive non-confronting and ambivalence accepting. Bridging into specific treatment can be appropriate. Open issues in this context are optimal strategies for communication, shared decision making, and psychoeducation including training and implementation of substance use medicine in the surgical facilities. The optimal architecture of a stepped care system is of great interest and might differ between health systems (VA/DoD 2009; NICE 24 2010; NICE 100 2010; NICE 115 2010; Spies et al. 2006b; Kork et al. 2010; Lange et al. 2011).

There is a risk of relapse ("drug reinstatement") in rehabilitated patients with a history of substance use and dependency after stressful events such as trauma or

surgery. Therefore, these patients should benefit from a careful and emphatic psychoeducation. They might need support also by addiction medicine professionals at some time after the event. This should be planned early.

As science and the health care develop rapidly, it is highly recommended to familiarize with today's guidelines ("systematically developed statements to assist physicians and, if necessary, other healthcare professionals and patients with decisions about appropriate health care in specific clinical circumstances") as only a systematic, formal, and group consensus approach is able to catch up with the developments in the field (Woolf et al. 1999).

111.2 Substance Use Disorders

111.2.1 Alcohol: Clinical Relevance

One of ten hospitalized surgical patients suffers from alcohol dependency; two might have an alcohol use disorder, and if they undergo surgery, they have more complications and length of stay is longer (Spies et al. 2001).

Among some patient groups, even higher rates of heavy drinking or alcohol dependency were reported: more than 25 % in patients with injury and 50 % of patients with aerodigestive system cancer. There is a variety in the clinical presentation of alcohol use-related morbidity in the different settings (e.g., younger trauma patient vs. older cancer patient vs. patients admitted for detoxification). Programs offered for the rehabilitation of addicted patients after detoxification might not attract other patient groups, e.g., young trauma patients. Even patients with addictions are rarely seen by addiction specialists, but frequently come in contact with health professionals in surgical or emergency units (Spies et al. 1996a, b, 2001b; Neumann et al. 2006; Neumann and Spies 2003).

AUD patients have a higher somatic and psychiatric morbidity: Postoperative or posttraumatic complications rate is two- to fivefolds higher. Chronic heavy drinking affects various systems as the nervous system, the cardiovascular system, the liver, the muscle, and the stress response and the immune system. The direct toxic effect of alcohol might be aggravated by malnutrition. Alcohol promotes carcinogenesis.

It has been consistently shown that patients who report heavy daily drinking (i.e., $>$60 g of alcohol) have an increased postoperative morbidity and more complications with increased postoperative healthcare use, including longer stays in the hospital and ICU and more second operations. Postoperative or posttraumatic morbidity is two- to fivefold increased: Infections and sepsis, cardiac complications (arrhythmia, congestive heart failure), bleeding and secondary hemorrhage, "acute respiratory distress syndrome" (ARDS), other surgical complications, alcohol withdrawal syndrome, and death occur more often. Therefore, length of stay is prolonged; requirement for critical care is increased. Also postoperative healthcare use is increased. Hospital and ICU stay is prolonged. Secondary operations are more often required. Already a consumption of more than two drinks a day has been associated in some reports with an increased risk. Interestingly, when diagnosing

dependency, information about consumption is not required (Tønnesen et al. 1992, 2009; Spies and Rommelspacher 1999; Spies et al. 1996a, b, 2001b; Moss and Burnham 2006; NICE 115 2011; Rubinsky et al. 2012).

111.2.1.1 The Scope of the Problem

Critically ill alcoholic patients are more likely to develop serious **infections** than nonalcoholic patients, especially nosocomial pneumonia, sepsis, wound, and urinary tract infections. Chronic alcohol abuse is also associated with an increase of ARDS (acute respiratory distress syndrome) and the severity of MODS (multiple organ dysfunction syndrome) in patients with septic shock.

Immune functions are altered by chronic heavy drinking. Stress response to surgical trauma induced by the hypothalamic-pituitary-adrenal axis (HPA axis) is augmented in AUD patients. A hypercorticolism was observed after surgical stress. Not only was hypercorticolism associated with complications, but a therapeutical suppression of the hypercorticolism at the level of the HPA axis reduced complications (Spies et al. 2006a). The skin response of the delayed-type hypersensitivity (DTH) is already reduced after surgical trauma due to associated stress. However, among alcoholic patients who undergo surgery, the DTH response was already reduced preoperatively compared with nondrinkers, and this impairment was exaggerated to a significantly larger extent postoperatively. This corresponds to other findings: Preoperatively, the T helper 1 to T helper 2 cells ratio is depressed in long-term alcoholic patients. This is predictive of later onset of infections. It remains suppressed after surgery. Postoperatively, the cytotoxic lymphocyte (Tc1/Tc2) ratio is also decreased in long-term alcoholic patients and remains depressed for 5 days. Correspondingly, the interleukin (IL)-6/IL-10 ratio and the lipopolysaccharide-stimulated interferon/IL-10 ratio in whole blood cells are decreased after surgery in long-term alcoholic patients. These anti-inflammatory changes in the postoperative period are predictive of subsequent postoperative infections.

Many other alterations of specific and nonspecific immune defense are reported that contribute next to other factors (e.g., smoking or aspiration) to the increased infection rate (Tønnesen et al. 1992, 1999; Spies et al. 2001b, 2004, 2006a; Sander et al. 2002; Moss and Burnham 2006; Lau et al. 2009).

Wound healing is impaired in heavy drinkers. Collagen and total protein accumulation in wound granulation tissue was impaired in treatment-seeking alcoholic patients, and proline and total protein increased significantly after 8 weeks of abstinence (Tønnesen et al. 1992, 1999, 2012; Spies et al. 1996a, b, 2001b).

The coagulation system can be affected even without clinical relevant alcoholic liver disease mainly by an altered thrombocyte function. Bleeding time can be prolonged. Beneficial effects of low-dose alcohol on cardiovascular disease have been related to these effects (Spies et al. 2001a; Tønnesen et al. 2009).

Heavy drinking can induce **cardiomyopathy**. A reduced ejection fraction can be found, which is often subclinical. However, heart rate can be increased and arrhythmias occur more often perioperatively. Cardiac morbidity is also increased due to arterial hypertension and the impact of smoking (Tønnesen et al. 1992, 1999; Spies et al. 1996a, b, 2001a, b, 2006a).

Table 111.1 Differential diagnosis of delirium or alcohol withdrawal syndrome: "I WATCH DEATH" (Adapted from Spies and Rommelspacher 1999)

I	Infections
W	Withdrawal
A	Acute metabolic
T	Trauma
C	CNS
H	Hypoxia
D	Deficiencies
E	Endocrinopathy
A	Acute vascular
T	Toxins/drugs
H	Heavy metals

Stress due to surgery and trauma, infection, or withdrawal has a wide range of effects. Next to the abovementioned immune suppression changes in body fluid composition, electrolytes, catecholamines, and hormones are relevant (Tønnesen et al. 1992, 1999, 2009; Spies et al. 1996a, b, 2001a, b; Neumann and Spies 2003; Moss and Burnham 2006).

Alcohol is **neurotoxic**. In higher dosage/doses it affects the central and the peripheral including the autonomic nervous system. It alters neuronal transmission. It induces tolerance and withdrawal. Alcohol use is also associated with neurotrauma. There are many reasons for cognitive impairment or delirium or "acute brain dysfunction" in emergency or critically ill patients with alcohol use disorders. In acute situations, other reasons for delirium (e.g., infection, trauma, or others) are often misinterpreted as intoxication or alcohol withdrawal syndrome (Table 111.1). The clinical presentation of critically ill patients with a history of alcohol and/or drug misuse may differ from other patients. Delayed diagnosis of AUDs or related comorbidity (e.g., alcohol intoxication and head trauma, withdrawal state, vitamin deficiencies, drug use, significant psychiatric disorders, infections, etc.) may have severe consequences (Tønnesen et al. 1992, 1999, 2012; Spies et al. 1996a, b, 1999, 2001b; Neumann and Spies 2003; Moss and Burnham 2006; NICE 115 2011).

Wernicke's encephalopathy should be suspected in all clinical conditions which could lead to thiamine deficiency, and intravenous thiamine (before any carbohydrate, 200 mg thrice daily) is indicated in these patients. It is often undiagnosed during lifetime. For diagnosis, two of the following four signs are required (EFNS guidelines, Galvin et al. 2010): dietary deficiencies, eye signs, cerebellar dysfunction, and either altered mental state or mild memory impairment. Total thiamine in blood sample should be measured prior to thiamine administration, if possible. MRI should be used to support the diagnosis of acute WE.

Re-trauma rate was also higher compared to patients without AUD. Trauma has, therefore, been described as a recurrent disease (Neumann et al. 2004, 2006).

111.2.1.2 Alcohol Intoxication

Alcohol is a central nervous system depressant. The clinical presentation of the alcohol intoxication ranges therefore from symptoms due to disinhibition like euphoria and agitation to a more global depression such as coma. Alcohol intoxication is potentially life threatening due to respiratory insufficiency, respiratory failure, aspiration, electrolyte disorders, rhabdomyolysis, hypoglycemia, temperature deregulation, and cardiovascular depression, with tachycardia and hypotension. The risk of trauma is high while intoxicated. A delayed diagnosis and treatment of other critical conditions such as trauma add to the high risk of alcohol intoxication (Neumann et al. 2003; Moss and Burnham 2006; NICE 100 2010; NICE 115 2011; NICE 24 2010).

111.2.1.3 Alcohol Withdrawal Syndrome

AWS is still a potentially life-threatening state. About half of all alcoholic patients in intensive care undergo an untreated alcohol withdrawal syndrome. It occurs frequently in intensive care patients after reduction of the sedation. The range and severity of the symptoms of alcohol withdrawal varies: cognitive thought disorder, hallucinations, convulsions, and sympathetic hyperactivity resulting from the imbalance of various excitatory and inhibitory neurotransmitter systems. The alcohol withdrawal syndrome is typically a diagnosis of exclusion. First signs are autonomic symptoms such as sweating, tremor, nausea, anxiety, and restlessness. Grand mal seizures can occur. Delirium tremens is characterized by spatial and temporal disorientations, hallucinosis, ataxia, tremor, and autonomic dysfunction. Many conditions can mimic AWS or might occur concomitant. Other disorders associated with delirium should be quickly ruled out or treated, including hemorrhage, metabolic disorders, infection, intoxication, hypoxia, pain, or focal neurological lesions. Mortality is related to the quality of the treatment: 15 % mortality when untreated vs. 2 % mortality when treated (Spies et al. 1996a, b, 1999, 2001a, b, 2003; Moss and Burnham 2006; Bråthen et al. 2005; NICE 100 2010; NICE 115 2011; NICE 24 2010; Awissi et al. 2013; Ungur et al. 2013).

111.2.1.4 Gastrointestinal/Metabolism

The **GI system** is impacted by alcohol in many ways: parenchymal liver injury (reduced synthesis, reduced enzyme activities, portal hypertension), hepatitis, gastritis, pancreatitis, enteral translocation, anorexia, malnutrition (substrates, vitamins, etc.), ulcers, gastrointestinal bleeding, autonomous dysregulation, and malnutrition.

Pharmacodynamic or pharmacokinetic interactions, increased toxicity of medication, and altered metabolism are complex and beyond the scope of this chapter. Chronic alcohol use alters metabolism (e.g., cytochrome P450 2E1 induction resulting in increased toxicity of paracetamol) or neurotransmitter function (e.g., alcohol and narcotics interfere on GABA receptor function). Clinicians use the manufacturer's information.

111.2.2 Diagnosis

111.2.2.1 Diagnosis

An early diagnosis is essential. However, the prevalence of AUD is consistently underestimated, particularly in women and younger patients: One out of 14 patients was diagnosed with AUD by an anesthesiologist during the preoperative assessment, but with a computerized questionnaire, detection rate was one out of six patients (Kip et al. 2008).

The diagnosis of an AUD is based on the synopsis of medical and substance use-related history, physical examination, and on self-report (like structured interviews such as questionnaires), if available. More information is provided by paraclinical findings (laboratory, imaging) and collateral information. In intubated and analgosedated or in emergency situations, patients' self-report might not be available. Markers are helpful when self-report is not available or valid, e.g., after trauma. A complication might be the trigger for considering an AUD. The information from markers of acute and chronic alcohol consumption as well as indices of alcohol consumption-related changes in organ function (e.g., liver enzymes, metabolic indices, immune dysfunction) can add further information. Patients might have an extra benefit from anonymous and confidential programs parallel to the routine patient care (Neumann and Spies 2003).

111.2.2.2 Questionnaires

Systematic screening with questionnaires is recommended, e.g., with the ten-item Alcohol Use Disorders Identification Test (AUDIT). The AUDIT was designed to cover a range of AUD severity from risky use to dependence. The full AUDIT asks next to the three consumption questions (AUDIT-C) also for indicators of addiction (three questions) and about alcohol use-related negative consequences (four questions). The ten AUDIT questions sum up to a score between 0 and 40 points. The test is considered as positive once more than 8 points are counted; however, lower cutoffs for women (e.g., 5 points) have been recommended. Lower cutoffs can increase sensitivity. Every combination of answers resulting in at least 5 points reflects at least one alcohol use-related problem. It takes about 2 min to apply the AUDIT in paper-and-pencil or computerized versions. The use of a computerized version detected much more patients in a preanesthetic clinic compared to the clinical routine (Neumann et al. 2004, 2006; Kip et al. 2008; VA/DoD 2009; NICE 24 2010).

The three-item "AUDIT-Consumption" questions (AUDIT-C) can be a shorter alternative. It provides a rough quantity x frequency estimate plus one question addressing binging (five or more drinks/occasion). It was found to be clinically useful. An increased AUDIT-C (>8 points) up to a year before surgery has been clearly associated with postoperative complications. A cutoff of 4 points (men) and 3 points (women) of the AUDIT-C was recommended for screening; however, this corresponds also to patterns of low-risk alcohol use like small amounts of alcohol with a meal (VA/DoD 2009; Neumann et al. 2004; Kip et al. 2008; NICE 24 2010; Bradley et al. 2011; Rubinsky et al. 2012). The NIAAA (see Fig. 111.1)

General algorithm and clinical pathway for patients with substance use disorders
Structured AUD, NUD and DUD screening

- Do you drink alcohol? yes:
  - Alcohol Use Disorder Identification Test (AUDIT), or
  - abbreviated version, AUDIT-C or
  - NIAAA screen for risky drinking e.g. How many times in the past year have you had…
    -5 or more drinks in a day (men)
    -4 or more drinks in a day (women) (One standard drink = 12–14g in the (US)
  - Plus CAGE (if dependence is of interest)
- Do you consume drugs, yes:
  - DSM-IV criteria or ICD criteria
- Do you smoke? Yes
  - Fagerström

If questionnaire results are negative, history not available, questionnaire screening not applicable or reliable and patient undergoing major surgery, critical ill etc.

- Consider collateral information
- Consider the use of markers
  Laboratory testing:
  AUD: CDT, GGT, MCV, EtG, Peth
  NUD: CO-Hb, Cotinin
  DUD: substance or metabolite testing in urine, saliva or blood (depending on substance)
- Comprehensive assessment of comorbidity

If patient is positive

- Synopsis of clinical findings (Screening, history, physical examination, questionnaires, marker, collateral information) =>
- Diagnosis (ICD 10, DSM 4/5) =>
- Consider and discuss specific interventions, include the informed patient into the decision making process (shared decision making), psychoeducation, if appropriate
  Prophylactic, preventive Intervention =>
  - (Preventive) treatment
    - Pharmacological withdrawal prophylaxis,
    - Substitution,
    - Stress reduction…
    - Treatment (e.g. AWS, detoxification, rehab, self help groups…)
    - Abstinence
  - Risk communication,
    - brief Interventions, e.g. Motivational Interviewing
    - FRAMES
      - Feedback
      - Responsibility
      - Advice
      - Menu of behavioral change
      - Empathy
      - Self - efficacy
- Monitor for complications
- Monitor for continuous risky/unrisky use

If preventive treatment not necessary:

- Inform, endorse, confirm
- Maintenance or supportive therapy in former substance users,
- Reevaluation of substance use screening negative patients in special medical conditions

AUD, alcohol use disorder; DUD, drug use disorder; NUD, nicotine use disorder (adop. and modified from Kork et al. 2010).

Fig. 111.1 General algorithm and clinical pathway for patients with substance use disorders

recommended the "Single-Item Alcohol Screening Questionnaire" as a screener (VA/DoD 2009).

CAGE ("cut down," "annoyance," "guilt," and "eye opener") is a four-item questionnaire. It is brief and easy to remember. The strength is detection of patients with dependence, but the sensitivity for risky, nondependent use has been considered as too low. Interestingly, the CAGE questionnaire can be used as a self-assessment tool (may be used in addition to an appropriate screening method to increase patient's awareness to unhealthy use or abuse of alcohol) (Neumann and Spies 2003; NICE 24 2010; VA/DoD 2009).

111.2.2.3 Laboratory

Biomedical markers may provide additive, objective information about acute or recent consumption, intoxication, relapse, heavy drinking, hazardous or harmful alcohol use, or possible use-related organ dysfunctions. Biomarkers cannot differentiate between AUD with and without dependency. So far, no single laboratory test (e.g., for acute abuse, alcohol in blood or breath; for abstinence, metabolites such as ethyl glucuronide (EtG); for chronic heavy drinking, gamma-glutamyl transpeptidase (GGT), mean corpuscular volume of red blood cells (MCV), carbohydrate-deficient transferrin (CDT), phosphatidylethanol (PEth)) is reliable enough on its own to support the diagnosis of an AUD. In the clinical context, they can add important information, especially when questionnaires are not applicable or reliable. As laboratory parameters for alcohol abuse, MCV, γ-GT, and CDT are used. Sensitivity of the markers (e.g., MCV 34–89 %, γ-GT 34–85 %, CDT 12 or less -94 %) as well as specificity (MCV 26–91 %, γ-GT 11–95 %, CDT 82–100 %) can vary considerably according to gender, age, setting, drinking pattern and prevalence of more severe AUD, the prevalence of comorbidity, and the AUD criterion used. Markers of increased alcohol consumption can also be increased by nonalcoholic organ damage, e.g., non-alcoholic liver disease (Neumann and Spies 2003; Hannuksela et al. 2007; Neumann et al. 2009).

Phosphatidylethanol (Peth) is formed only in the presence of alcohol. It has reported sensitivities of 97–99 % and specificity of 100 % when differing heavy drinkers (60 g/day of alcohol and much more) from controls. However, the cutoff is not clear yet and Peth is not yet part of clinical routine. More research is needed to establish the role of this marker of chronic heavy drinking. Storage can be problematic, relevant in vitro formation and degradation has been described (Hannuksela et al. 2007; Niemela 2007 CCA).

Sensitivity of markers can be lower, when patients reduce their alcohol consumption preoperatively. Another reason for false-negative findings are blood loss and volume replacement in critically ill patients (e.g., after severe trauma; therefore, sampling of the blood should be done as early as possible, e.g., at admission or in the resuscitation room) (Spies et al. 2001; Hannuksela et al. 2007; Neumann et al. 2003).

Sensitivities, specificities, and predictive values vary considerably between the studies according to patient and control group characteristics and differing alcoholism criteria (Neumann and Spies 2003). In patient groups with a high prevalence

of severe AUDs, in older patients, and in patients with a continuous daily consumption (in contrast to occasional binge drinking), the sensitivity is usually higher, whereas comorbidity might interfere with specificity (Neumann and Spies 2003).

Percent CDT (CDT/total transferrin ratio) levels were elevated in patients drinking 50–80 g/day or more. Elevated values were found also among patients with end-stage liver disease and genetic variants. Total CDT levels are additionally affected by factors that raise transferrin levels such as iron deficiency, chronic illnesses, and menopausal status. The roles of female gender, low body mass index, chronic inflammatory diseases, and medication on CDT levels require further study. Sensitivity can be lower in women and patients with episodic heavy drinking or cutting down for some time and acute blood loss. Therefore, CDT should be determined early after admission (Neumann and Spies 2003). Early sampling in the emergency room and before volume resuscitation increased the sensitivity from 65 % to 74 % for CDT. Complication rate was increased in trauma patients with increased CDT (increased CDTect, absolute CDT values, Spies et al. (1998), discussed in Neumann and Spies 2003; %CDT, McKinzie et al. 2010).

Furthermore, the determination of markers of acute consumption (alcohol in blood, urine, breath) or markers of recent use (e.g., ethyl glucuronide , ethyl sulfate, urinary 5-HTOL/HIAA) can add important information of recent consumption and hangover. Blood, breath, or urine alcohol is detectable for several hours; however, metabolites are detectable for longer (e.g., EtG up to 80 h) even after consuming smaller amounts. They can be used to monitor abstinence (e.g., in obstetrics or liver transplantation). Alcohol consumption in the evening before surgery is related to postoperative morbidity. These biomarkers are usually not available as a point-of-care application except breath alcohol. There are unsolved methodological issues concerning cutoffs and possible reasons for false positives. Therefore, markers cannot be used without the clinical context (Neumann and Spies 2003; Hanunksela et al. 2007).

The determination of the blood alcohol concentration (BAC) is considered as standard in trauma care: Between 16 % and 39 % of trauma victims were BAC positive on admission, and 55–75 % of injured patients who were BAC positive had an alcohol abuse or dependence diagnosis. However, a substantial number of trauma patients with AUDs (11–45 %) are BAC negative (Runge et al. 2001; Neumann et al. 2003). A high blood alcohol concentration indicates tolerance, which itself is linked to dependence. Alcohol metabolites such as ethyl glucuronide may be used for monitoring abstinence since they can be detected for a longer period than alcohol from blood or urine. So far some promising markers are not available as a point-of-care application (Neumann and Spies 2003).

Other indices of altered organ function (e.g., liver enzymes, metabolic indices, immune function parameters) might add valuable information. These surrogate markers give valuable insights into the impact of AU on organ function (e.g., immune response) and might guide therapeutical interventions, but are not considered as alcohol abuse markers per se (Neumann and Spies 2003; Spies et al. 2004, 2006; Lau et al. 2009).

111.2.2.4 Screening and Diagnosis

All patients should be screened for AUD in a systematic approach in order to detect those patients who might benefit from evidence-based strategies to minimize the risk for a complicated perioperative clinical course. The use of an alcoholism-related questionnaire is recommended.

If self-report is not possible, not reliable, or negative, markers and collateral information should be used. All patients:

- Scoring positive (AUDIT: men $\geq$ 8/women $\geq$ 5).
- Scoring below the cutoff in a questionnaire or from those where a reliable history and/or questionnaire cannot be taken **and** with one or more positive biomarkers should undergo further assessment (Kip et al. 2008; Kork et al. 2010).

Confirmatory assessment includes a history of alcohol and substance use and consumption pattern, comorbidity, and the criteria for hazardous use or dependence (DSM/ICD); however, absence of earlier withdrawal symptoms does not exclude the possibility of an exaggerated stress response or withdrawal. Patients screened positive for AUD should further be evaluated in an interdisciplinary approach.

A clinically relevant alcohol abuse is defined in operative medicine as an intake of $\geq$ 60 g/day of alcohol; however, risky consumption has been defined as 30 g/day (men) or 20 g/day (women). High-risk patients with two or more positive biomarkers from different pathophysiological backgrounds are obvious candidates for preventive strategies (Neumann and Spies 2003; Tønnesen et al. 2009; Spies et al. 2001).

Consulting a specialist in substance abuse may be appropriate in order to provide advice on how to reduce long-term risk, e.g., to achieve abstinence. All patients being considered for high-risk surgery or having had a trauma should be offered counseling focusing on risk factors in relation to the operative treatment, diagnosis, and prognosis (e.g., in the preanesthetic evaluation). Alcohol is a risk factor. Especially in patients consuming 60 g of alcohol or more daily, options (e.g., remain abstinent for up to 4 weeks before elective surgery or receive preventive perioperative pharmacological prophylaxis targeting the stress response or withdrawal) should be discussed. Information and feedback on any pathological finding-associated alcohol consumption may contribute to the diagnosis. The patient-oriented communication style is ambivalence accepting, not confrontive, emphatic, but directive; one aim is a working alliance with the patient. It includes a feedback and advice about the risks and opportunities and it addresses patient's responsibility. Through these (brief) interventions longer-term changes in motivation might be achieved (Spies and Rommelspacher 1999; Neumann and Spies 2003; Neumann et al. 2004, 2006; Tønnesen et al. 1999, 2009).

One has to be aware that some patients are under triple stress during the evaluation: an operation, an AUD diagnosis, and the fear of stigma. Waiting patiently and reevaluating later can be an option. Approaching patients three times instead of one time before surgery doubled detection rate. The combination of laboratory markers and the CAGE questionnaire and up to three consultations can increase the detection rate from 16 % by clinical routine alone to 91 % in

surgical patients scheduled for upper digestive tract surgery (Martin et al. 2002). Markers might be used also as biofeedback. The patient might have a benefit to learn about the risk associated with a positive marker and the gain in health, when the marker normalizes (Neumann and Spies 2003). More research is needed to determine the value of biomarkers in the context of clinical decision-making algorithms.

111.2.3 Treatment and Prevention

111.2.3.1 Screening and BI

A brief intervention should be delivered at the point of care to all AUD patients, e.g., in the preanesthetic clinic. This approach is recommended by current guidelines. A consistent reduction of alcohol consumption by brief interventions was reported in primary health care, mainly in men. Also brief interventions were generally effective in hospital patients; however, some inconsistency was observed, especially in emergency settings (NICE 24 2010; NICE 115 2010; VA/DoD 2009). Effective screening and brief intervention strategy (feedback, advice, tailored information) can be provided by computer in many clinical settings (Neumann et al. 2006; Kip et al. 2008; Lange et al. 2011). A computerized questionnaire and brief report on lifestyle issues for surgical patients is available as a tool for quality management in Germany. It is applied by the German Anaesthesiological and Intensive Care Society (current access: http://www.dgai-lsa.de; username: HAI2008; password: dgai; Kork et al. 2010).

111.2.3.2 Choice of Anesthetics

Anesthetics should be given according to the clinical effect. As alcohol and inhalation agents as well as hypnotics work synergistically on the $GABA_A$ and on other receptors (NMDA, glycine) in intoxicated patients, a dose reduction is necessary as well as an increase in dosage in the withdrawal state. Muscle relaxants that are metabolized hepatically might have a prolonged effect in patients with a hepatic insufficiency; neuromuscular monitoring is recommended. Alternatives would be atracurium and cis-atracurium as relaxants. Alcohol consumption is not a contraindication for the use of inhalational anesthetics. Sevoflurane is normally metabolized to <5 % in the liver. However, also the induction of CYP2E1 could lead to an increased formation of plasma fluorides. Due to the small intrarenal metabolism of sevoflurane, nephrotoxic effects are not expected, but there are no studies on AUD patients at risk.

Regional anesthesia should be used only in patients able to cooperate and with adequate vigilance. The coagulation should be monitored and a careful history of coagulation disorders and medication that interferes with the coagulation should be obtained. Limitation for regional method is agitation of the patient and the lack of protection of the respiratory tract. In the phase of intoxication, regional procedures are contraindicated (Klotz and Ammon 1998; Neumann et al. 2003).

111.2.3.3 PACU

The patient can be transferred from the recovery room to the ward when sufficiently vigilant, cardiopulmonary stable, and pain-free. Monitoring for delirium is recommended (NuDesc, DDS, CIWAr). Regular monitoring includes the acid-base balance, electrolyte levels, and blood glucose levels. Hypokalemia and hypomagnesemia can occur during the early withdrawal. Inadequate drainage losses can be a sign of a coagulation dysfunction. In patients sobering up, acetaminophen should be used with caution (Martin et al. 2010; Spies et al. 1999, 2003; Otter et al. 2005; Riordan and Williams 2002; Moss and Burnham 2006).

111.2.3.4 Postoperative Treatment

It is not possible to draw a clear line between prevention and treatment of alcohol withdrawal syndrome. Both prophylaxis and treatment should be carried out symptom-guided in time (Spies and Rommelspacher 1999; Spies et al. 2003). All patients are therefore closely monitored by means of the "Revised Clinical Institute Withdrawal Assessment for Alcohol Scale" to monitor or compare scores used in intensive care (e.g., CAM-ICU, DDS, Lütz et al. 2010; Martin et al. 2010; Otter et al. 2005).

111.2.3.5 Therapy of Alcohol Withdrawal Syndrome

The diagnosis of an alcohol withdrawal syndrome can be made if other causes of delirium or complications such as bleeding, metabolic dysfunction, infections, ischemia/hypoxia, pain, or focal neurological symptoms are excluded (Table 111.1). Patient's history or laboratory tests should indicate an AUD. Alcohol withdrawal syndrome should be treated early. The severity of AWS in critically ill surgical or trauma patients as reflected by CIWA-Ar, however, is several times higher in ICU patients compared to psychiatric patients. The complex interactions between anesthesia, postoperative stress, trauma, infections, and other factors may enhance imbalances of transmitter systems and require a more effective therapy. The symptoms have to be closely monitored (Awissi et al. 2013; Moss and Burnham 2006; Martin et al. 2010; Spies and Rommelspacher 1999; Spies et al. 2003; Ungur et al. 2013).

If an alcohol withdrawal syndrome occurs, the use of more than one drug should be considered. Treatment should be symptom oriented: for agitation and seizures, benzodiazepines (first substance of choice, e.g., lorazepam, diazepam); for autonomic hyperactivity, alpha-2 agonists (clonidine or dexmedetomidine); and for hallucinations or productive-psychotic symptoms, neuroleptics according to the underlying transmitter imbalances: GABAergic (e.g., benzodiazepines, clomethiazole), dopaminergic (e.g., haloperidol), and noradrenergic system (e.g., clonidine). Dosage should be adjusted to the patient's clinical condition. Ethanol is obsolete in the manifest withdrawal state (Amato et al. 2011; Awissi et al. 2013; Spies and Rommelspacher 1999; Spies et al. 2003; Ungur et al. 2013).

Any delay or inadequacy of therapy may worsen symptoms. In contrast to a fixed-dose treatment, symptom-oriented treatment using a scoring system reduces time of treatment, can shorten the clinical course of AWS, and can reduce morbidity

use of medication, complication rates, time of ventilator support, and length of ICU stay when compared to a preassigned and fixed treatment plan. Different scores can be used in order to monitor delirium and to guide therapy. CIWA-Ar score was validated for normal wards, whereas the Delirium Detection Score (DDS) was validated for the ICU setting (Otter et al. 2005; Spies et al. 2003; Moss and Burnham 2006; Martin et al. 2010; Awissi et al. 2013; Ungur et al. 2013).

If simultaneously clonidine and haloperidol are used in the treatment of alcohol withdrawal syndrome, hypokalemia and hypomagnesemia should be avoided, as this can cause QT prolongation and arrhythmias. Clonidine can cause hypotension, bradycardia, AV block, and constipation. Electrolyte disorders should be treated, especially hypokalemia and hypomagnesemia (Moss and Burnham 2006; Spies and Rommmelspacher 1999).

111.2.3.6 Prophylaxis

Drugs used to prevent withdrawal are benzodiazepines, clomethiazole (per os), clonidine, and haloperidol or risperidon, usually in dosages that are lower than used for treatment. If indicated, a long-acting benzodiazepine can be given the evening before surgery (e.g., lorazepam) for premedication and a short-acting benzodiazepine in the morning of surgery (e.g., midazolam). In patients not adequately premedicated before the induction of anesthesia, midazolam IV can be titrated to the desired effect; additionally clonidine, haloperidol, or ketamine can be given intravenously, if there are no contraindications. The prevention of alcohol withdrawal syndrome on a peripheral ward is usually done with a single substance. Monitoring on the ward is required. If the requirement for monitoring is not met by the ward's resources, the patient must be moved to a monitoring or intensive care unit. It is important to reduce prophylactic dosage after symptom control, as this – in unintended continued treatment – includes even a potential for addiction. Preventive treatment may avoid AWS or attenuate its severity; transition from prevention to treatment is continuous (Spies and Rommmelspacher 1999; Spies et al. 2006).

In alcoholic patients, hypercortisolism can occur postoperatively after surgical stress. Pharmacological intervention by inhibition of the HPA axis (stress prevention) with morphine, low-dose ketoconazole, and ethanol in alcoholic patients could prevent the prolonged cortisol response to surgical stress, compared with placebo, and thus reduce the incidence of infection Spies et al. (2006a). For blockade of the HPA axis and to reduce infectious complications, perioperative infusion of low doses of ethanol (0.5 g/kg/day IV) or low-dose morphine (15 μg/kg/h) has been shown to be effective in one study. As this is not a sufficient pain treatment, pain should be monitored by visual analog scale (VAS) or numerical rating scale (NRS) and treated according to evidence-based hospital standards (Spies et al. 2006; Martin et al. 2010).

Perioperative administration of prophylactic medication, especially alcohol, requires an assessment of the motivation regarding a change in alcohol consumption and informed consent after shared decision making. Risk and options are communicated. This communication should have a big overlap with motivational interviewing and change talk (Kork et al. 2010).

111.2.3.7 Treatment of Wernicke's Encephalopathy

Intravenous thiamine (before any carbohydrate, 200 mg thrice daily) is indicated for the treatment of suspected or manifest WE. Oral substitution is initially inadequate. Hypoglycemic patients should receive thiamine latest when administering intravenous glucose (Galvin et al. 2010).

111.2.3.8 Preoperative Abstinence

Pathophysiological dysfunctions due to heavy drinking are potentially reversible. Immune response, stress response, alcoholic cardiomyopathy, bleeding time, frequency of hypoxia, and wound healing improve during abstinence within a time frame of weeks or months (Tønnesen et al. 2009; Spies et al. 2001a).

Two studies from Denmark (one among nondependent alcohol consumers (60–420 g/day) undergoing radical colorectal resection patients and one that included elective hip arthroplasty patients) showed an effect of 4-week preoperative abstinence and psychosocial counseling combined with disulfiram substitution on the overall complication rates including infection rate. Postoperative morbidity was reduced from 74 % to 31 % after colorectal surgery. There was no significant reduction of in-hospital and 30-day mortality (Tønnesen et al. 2009; Oppedal et al. 2012).

111.2.3.9 Addiction and Psychosocial Treatment

The alcohol-dependent patient should be seen early by an addiction specialist. The indication of ambulatory or inpatient detoxification before or after surgery should be evaluated. Alcohol-dependent patients may profit from anti-craving medication such as acamprosate, naltrexone, or alcohol deterrent medication such as disulfiram. Naltrexone can interfere with postsurgical pain therapy, if opioids are indicated. One large multicentre study by Anton et al. (2006) underlined the importance of medical management (Spies and Rommelspacher 1999; Anton et al. 2006; Tønnesen et al. 2009; Kork et al. 2010).

111.3 Tobacco Dependency, Nicotine Use Disorder (NUD)

As tobacco use is associated with cancer and cardiovascular or pulmonary diseases, smokers are overrepresented among these patients. Accordingly, the incidence of perioperative pulmonary complications, cardiovascular complications, impaired wound healing, and wound infection is increased. Smokers, who continue to smoke until surgery, have a higher two- to sixfold pulmonary morbidity compared to nonsmokers (Bluman et al. 1998; Møller et al. 2002; Tønnesen et al. 2009).

Smoking is usually reported spontaneously. Standardized questionnaires such as the Fagerström Test evaluate degrees of dependency and were used to guide therapy, e.g., nicotine replacement therapy. Different from the construct of the ICD or DSM dependence definition, the number of cigarettes is needed for a positive score (Heatherton et al. 1991).

An established point-of-care biomarker of acute smoking is carbon monoxide-hemoglobin (COHb). It is routinely determined in anesthesiology workplaces. CO binds to the hemoglobin and reduces the oxygen binding capacity of the hemoglobin significantly (up to 15 %). This might cause hypoxia even in patients without coronary heart disease and is associated also with wound complications. COHb predisposes for ST-segment depressions in stress situations. In addition, increased nicotine levels are associated with an increased sympathetic activity: There is an increased heart rate, increased blood pressure, and a reduced peripheral blood flow through vasoconstriction. Increased oxygen consumption meets a lowered oxygen supply. The net effect might result in a relative hypoxia. In patients with coronary heart disease, the incidence of myocardial ischemia increases significantly. Patients smoking immediately prior to surgery with elevated expiratory CO concentration (>35 ppm) showed more ST depressions. The half-life of COHb and nicotine is about 12 h, e.g., after abstaining overnight. In cardiac risk patients, an abstinence of 12–48 h reduces perioperative cardiac morbidity. A perioperative smoking cessation of 12–48 h is required (Zwissler and Reither 2005; Neumann et al. 2008; Tønnesen et al. 2009; Kork et al. 2010). COHb in blood was an excellent marker to detect current smoking in trauma patients. The cutoff of COHb should be lowered to 1.6 % in women and to 1.8 % in men (Neumann et al. 2008).

The pulmonary morbidity is two- to sixfold higher in patients smoking until the surgery. In smokers, the lung capacity and ciliary function are reduced; closing capacity is increased. The production of mucus is increased, but the secretion of pulmonary clearance reduced. This can also affect otherwise asymptomatic younger smokers. This is associated with an elevated pulmonary postoperative morbidity. In smoking patients undergoing elective surgery, pulmonary complications were 22 % vs. 5 %. In abdominal surgery, the rate may be even higher. Smokers are more frequently admitted to ICUs than nonsmokers (Zwissler and Reither 2005; Møller et al. 2002; Tønnesen et al. 2009).

Smoking lowers the pressure in the lower esophageal sphincter; however, this effect is fully reversible after 5 min. The emptying of solid but not liquid food particles from the stomach is delayed after smoking. In respect to acute smoking, there is no increased risk of aspiration neither to gastric volume nor to the acidity of the gastric juice. However, smokers experience less postoperative nausea and vomiting (PONV) (Zwissler and Reither 2005).

Smoking impacts on the immune function. This leads to an increased risk of infections. The immune system recovers after 2–6 weeks of abstinence from smoking, wound healing after 3–4 weeks, and the lung function after 6–8 weeks (Tønnesen et al. 2009).

More intensive smoking cessation programs are more effective than briefer interventions; however, briefer interventions might bridge the patient into more intensive programs that include nicotine replacement therapy (NRT), CO monitoring, and psychoeducation and counseling about the expected advantages and disadvantages of abstinence, side effects, withdrawal symptoms, diet and exercise, weight gain, and other issues. Six randomized trials have been published that evaluated preoperative smoking cessation with abstinence rates between 40 %

and 89 %. Three studies suggest that preoperative smoking cessation programs of 3–4 and 6–8 weeks duration are beneficial in respect to complications. Shorter periods of abstinence are not disadvantageous. A potential negative effect of a preoperative smoke stop had been reported in retrospective studies with considerable methodological weaknesses. Also postoperatively nicotine replacement is recommended, adapted to the degree of nicotine dependence (Fagerström test) (Bluman et al. 1998; Møller et al. 2002; Lindström et al. 2008; Sørensen and Jørgensen 2003; Tønnesen et al. 2009).

Wound healing is affected by smoking. Collagen production is impaired. The wound infection rate of sacral incisions in 78 volunteers was lower at 4–12 weeks after randomization, compared with smokers without cessation, but not after a week examined. No difference was observed between placebo and patch therapy (Sørensen and Jørgensen 2003; Møller et al. 2002; Tønnesen et al. 2009).

Nicotine represents a cholinergic agent. Therefore, in case of surgery without preoperative abstinence, nicotine replacement therapy (NRT) and other cholinergic agents like physostigmine are an option in these patients as adjunctive for treatment of pain and the potential of saving postoperative opioids. Perioperative NRT initiated before induction of anesthesia and maintained after surgery should be considered. Physostigmine 1.5 mg IV at the end of surgery then 1 mg/h for 24 h can be given as an cholinergic agent and for pain reduction, if no NRT was started. Cholinergic agents are basically emetogenic; PONV prophylaxis might be necessary (Møller et al. 2002; Beilin et al. 2005; Kork et al. 2010).

111.4 Opioids

111.4.1 Clinical Relevance

Patients with opioid dependency undergoing surgery might be polysubstance users with significant comorbidity or chronic pain patients treated with opioids. They are at risk for withdrawal. Complex individualized treatment strategies are required. Many patients were seen in emergency facilities. The effects of opioids are enhanced by CNS depressant drugs, e.g., ethanol and GABEergic medication. Respiratory depression (with aspiration (pneumonia), cyanosis, and/or pulmonary edema) and consecutive hypoxia are the most common causes of morbidity and death after acute opioid intoxication. This is associated with ST-segment changes, tachycardic arrhythmias, hypotension and congestive heart failure, and cerebral and spinal ischemia or nerve compression syndromes and muscle damage with consecutive crush syndrome or rhabdomyolysis after immobilization when intoxicated. Patients might suffer from acute and chronic infections including HIV and hepatitis, intravenous and polysubstance drug use-associated bacteriemia, heart valve pathologies, atherosclerosis from smoking, trauma, and psychiatric comorbidity. Peripheral and central venous access is often difficult (Hernandez et al. 2005; Kork et al. 2010). Relevant withdrawal symptoms are tachycardia, diarrhea, hyperhidrosis with dehydration next to mydriasis, and goose bumps.

111.4.2 Perioperative

Opioid-dependent hospital patients should receive a basal substitution ("baseline") with methadone or racemate plus opioids as clinically required for analgesia under the control of the vital signs and withdrawal parameters. Regional anesthesia alone or in combination with general anesthesia, NSAIDs, alpha-2 agonists (clonidine, lofexidine), and ketamine can be considered. Postoperatively, the need for analgesia can be increased in drug-dependent patients. Partial agonists (e.g., buprenorphin) should be avoided. Treatment should be symptomatic, e.g., NSAIDs, alpha2-agonists (clonidine, lofexidine) (APA 2006; Kork et al. 2010).

Clinical signs of over- and underdosage should be observed. Vital signs and symptoms of withdrawal (e.g., Objective and Subjective Opiate Withdrawal Scale, OOWS, SOWS) should be documented regularly. Written bedside standard operating procedures should clearly describe:

- In case of overdose: command breathing; administer oxygen and ventilation, eventually titration of naloxone.
- In underdosing: rescue medication (give opioids).

QTc time (ECG) has to be monitored. Under methadone medication, the QTc time can be prolonged, which is a risk factor for arrhythmias (APA 2006; Kork et al. 2010).

Laxatives (e.g., lactulose) are administered as adjuvant until the stool consistency has normalized. Adequate hydration replaces volume loss in hyperhidrosis (e.g., during withdrawal). Diverse drug interactions must be considered in patients with methadone substitution therapy. Methadone interaction with other medications should be anticipated. Manufacturer's information should be consulted, as enzyme induction (cytochromes) or inhibition concerns a variety of substance, (e.g., antiviral medication, carbamazepine, phenytoin, cimetidine, and rifampicin). Medication with sedating properties (e.g., benzodiazepines) can act synergistically and can cause respiratory depression. Partial antagonists (e.g., buprenorphine) can trigger withdrawal symptoms and are contraindicated in this case. Clonidine and lofexidine attenuate heroin or methadone withdrawal symptoms more effectively than placebo and can be perioperatively or intraoperatively applied once hemodynamic monitoring is available (Hernandez et al. 2005; APA 2006; Gowing et al. 2009; Kork et al. 2010). The pain treatment **in former opioid-dependent patients** is an understudied issue. There are concerns that this may trigger a relapse ("drug reinstatement") when mu agonists (or other psychoactive drugs) are potentially indicated in the perioperative period. Regional anesthesia or general anesthesia combining inhalation anesthetics with N2O, ketamine, and nonsteroidal anti-inflammatory drugs is not always possible. If indicated, titration of adequate amounts of a short-acting μ-agonist can be necessary; alpha-2 agonists can relieve withdrawal symptoms. Patients should be carefully informed (e.g., about craving) and educated about the small but relevant risk of relapse. This should be documented, and written informed consent should be obtained. Possible treatment options should be discussed, including post-hospital psychosocial and medical care. Any relapse is a potentially life-threatening situation. Opioid-related death occurs

often in former users. Some patients seem to be unaware of the decreased tolerance and use opioids in usual doses. Patients should be educated about these phenomena (Kork et al. 2010).

In the first days of the postoperative period, opioid substitution therapy is continued. In addition, opioids are administered for analgesia. Increased demand in comparison to "opioid-naive" patients can be expected (Kork et al. 2010).

In the emergency situation, preoperative switching to methadone is not possible in opioid-dependent patients. Symptomatic patients are treated if necessary and the presence of withdrawal symptoms with a μ-agonists. A regional anesthesia should be considered (Kork et al. 2010).

The consequences of drug-induced respiratory depression with consequent hypoxia or atelectasis, aspiration, cardiovascular symptoms, neurological symptoms, nerve compression and damage, and polysubstance comorbidity have to be evaluated. Next to the ABCDE (airway, breathing, circulation, disability, evaluation) approach, an ECG, cardiac enzymes, echocardiography, chest X-ray, imaging, lab and drug screening, and neurological and psychiatric evaluation are helpful (Hernandez et al. 2005; Kork et al. 2010).

Naloxone carefully titrated is one option to treat overdose. This is also helpful to establish the diagnosis. The effect of naloxone lasts only about 30–60 min. In emergency situations, naloxone administration can be potentially harmful. The initiation of (immediate) withdrawal stress in patients with impaired organ function is potentially dangerous. Craving-associated drug-seeking behavior in the emergency situation after antagonist administration can cause difficult situations. Trauma or impaired organ function, severe prolonged hypoxia, suicide intention, or intake of other CNS depressants that are non-mu agonists cannot be ruled out. Cases of pulmonary edema have been reported after naloxone treatment. Intubation and ventilation by skilled personal might be of lesser risk (Osterwalder 1996; Kork et al. 2010).

Complex psychiatric and somatic morbidity requires individualized psychosocial and medical care. Brief intervention might bridge into more intensive treatment. Detoxification should be carefully planned, (e.g., cold, agonist assisted, symptomatic treatment, or opioid antagonist induction therapy (naltrexone), e.g., under anesthesia (APA 2006).

The opiate antagonist-induced withdrawal under anesthesia is indicated only in special cases and is not associated with a better outcome. This method must be performed under ICU conditions. Opiate antagonist application induces a pronounced withdrawal syndrome with an increase in catecholamine and a strong cardiovascular stimulation in opioid-dependent patients. Severe hypokalemia may occur. In published protocols, multiple doses of naltrexone were administered intragastral during several hours under general anesthesia. Relevant other side effects are severe electrolyte disorders, nausea, gastric reflux, diarrhea, and muscle and stomach pain. The procedure continues until the withdrawal symptoms have subsided or a negative challenge test (intravenous administration of naloxone). The naltrexone maintenance treatment should be carried out for several months in an interdisciplinary psychosocial treatment approach (APA 2006; Brewer et al. 1998; Hensel and Kox 2000; Kork et al. 2010; Schmidt et al. 1998).

111.5 Cocaine

111.5.1 Clinic

The central and peripheral reuptake inhibition of norepinephrine, dopamine, and serotonin is responsible for the stimulatory effects of cocaine resulting in a stimulation of the CNS and the sympathetic system with pronounced cardiovascular and cerebrovascular effects and related complications. It has also a local anesthetic effect. The pathogenesis of ischemic complications is multifactorial: increased oxygen demand with a fixed or limited myocardial oxygen supply, myocardial vasoconstriction, and increased platelet aggregation tendency. By the chronic use of cocaine, there is a depletion of dopamine and other neurotransmitters and a decrease in dopamine receptors D2. This is associated with depression and the so-called crash. Therefore, all patients with a history of cocaine as well as stimulant use should be carefully evaluated, especially for cardiovascular and neurological morbidity (Egred and Davis 2005; Hernandez et al. 2005; Hollander and Henry 2006).

111.5.2 Therapy

Treatment of patients with chest pain and ECG changes includes oxygen, benzodiazepines, nitrates, and acetylsalicylate. Benzodiazepines can reduce the elevated blood pressure, tachycardia, and anxiety. Calcium channel blockers and alpha-blockers may be given in addition. Beta-blockers without alpha-blockade are contraindicated for the treatment of cocaine-induced hypertension and tachycardia. They increase the cocaine-related mortality, possibly due to increased α-adrenergic stimulation, e.g., coronary spasm. The 1-selective blocker esmolol along with an infusion of sodium nitroprusside or the administration of calcium antagonists can be used. The indications for thrombolytic therapy should be made cautiously in the context of cocaine use. If symptoms persist, catheter revascularization seems to be safer (Egred and Davis 2005; Hernandez et al. 2005; Hollander and Henry 2006).

111.5.3 Urgent and Emergency Intervention

Cocaine is rapidly metabolized and is therefore difficult to detect in the blood, but it can be detected in the urine up to 6 days after ingestion. The sympathomimetic effect may persist beyond the actual phase of intoxication. A cardiopulmonary and neurological evaluation should be performed. A drug screening reveals drug use. In addition to injuries, often associated with violence, chest pain is common among cocaine-induced symptoms in the ED patients. Cardiac troponin I or T is more specific compared to the CK-MB or even myoglobin for acute myocardial infarction after cocaine use. There is a high rate of false-positive myoglobin and creatine kinase values, especially in rhabdomyolysis. Acute cocaine ingestion can have cardiotoxic effects and is related to sudden death. ECG findings are abnormal in

56–84 % of patients with cocaine-associated chest pain. It should be noted that the sensitivity of the ECG is only 36 % and specificity is 90 %. Regional anesthesia during cocaine intoxication is not recommended because local anesthetics have similar pharmacological effects as cocaine and might potentiate toxicity. If general anesthesia is required in an urgent situation, avoid the potentiating substances, e.g., adrenergic stimulants, ketamine, etomidate, aminophylline, MAO inhibitors, tricyclic antidepressants, acetylcholinesterase inhibitors, muscle relaxants with autonomic side effects, local anesthetics, and volatile anesthetics with stimulating properties. The sympathomimetic effect of cocaine can make the assessment of the intravascular volume or blood loss difficult, so more extended monitoring next to arterial (and central venous) pressure measurement and monitoring of urine and hemodynamic stabilization before induction of anesthesia is important. As part of the intensive inpatient treatment, possible withdrawal symptoms are observed. Cerebral blood flow is reduced. First signs are lower blood pressure, hypothermia, and miosis. Benzodiazepines and clonidine can be considered (Egred and Davis 2005; Hernandez et al. 2005; Hollander and Henry 2006).

111.5.4 Elective Procedure

Patients with cocaine abuse have a higher risk of cardiovascular disease, also after the intoxication phase. The sympathomimetic effect can be prolonged and withdrawal also can be a risk for a cardiovascular event. Benzodiazepines in an adequate dosage can be given for premedication. Any stimulating medication should be used with caution, including those inhalation anesthetics or muscle relaxants such as pancuronium with autonomic side effects that sensitize the myocardium to catecholamines. The total intravenous anesthesia is preferred (Egred and Davis 2005; Hernandez et al. 2005; Hollander and Henry 2006).

111.6 Other Drugs

It is beyond the scope of this chapter to describe all specific features of abused drugs with an addictive potential relevant for anesthesia. Synthetic drugs are increasingly used. Clinically important is a heterogeneous group of stimulatory, entactogenic ("touching the inside"), hallucinogenic, or hypnotic drugs with overlapping properties. As a general rule, symptomatic treatment, screening for drug use, and consulting expert help (e.g., poison control center) can be recommended for critically ill patients with suspected drug use. A systematic diagnostic approach might reveal unexpected morbidity, as acute and chronic use has been related to a wide spectrum of neurological, cardiovascular and pulmonary, metabolic, and infectious/immunological complications even in younger undergoing smaller procedures: Diagnostic strategies that include, e.g., a full lab, drug screen, echocardiography, or imaging, should be considered early. Patients with suspected intoxication should be monitored

continuously. Street drugs may be mixed with many other relevant substances (Steadman and Birnbach 2003; Hernandez et al. 2005). Many patients use more than one drug, e.g., many self-medicate in order to overcome withdrawal symptoms, such as "the crash" that comes after taking stimulants or sedatives. A distinction between intoxication, withdrawal, and neurological insult is often difficult, and important other causes for delirium should be ruled out (Table 111.1, Kork et al. 2010; Spies and Rommelspacher 1999).

111.6.1 Stimulants, Entactogens, and Hallucinogens

Ecstasy (e.g., MDMA), amphetamines, and LSD act more or less stimulating. Tachycardia, hypertension, dizziness, panic attacks, or visual illusions can occur. Clinical important complications are cardiac arrhythmias, hyperthermia, renal failure, hepatotoxicity, multiorgan failure, rhabdomyolysis, hyponatremia and cerebral edema, seizures and intracranial hemorrhage, altered consciousness, or sudden death (Hernandez et al. 2005; Hall and Henry 2006). When used in dance marathons, extreme dehydration and hyperthermia up to 42 °C might occur or hyponatremia due to excessive water intake. Cerebrovascular accidents and complications due to acute anxiety and panic disorders may also occur (Hernandez et al. 2005; Hall and Henry 2006).

111.6.2 Treatment of Acute Intoxications

The treatment of acute stimulant intoxication is symptomatic. Dehydration and hyperthermia is treated with external and internal cooling, rehydration, antipyretics, correction of electrolyte imbalance and (metabolic) acidosis, and sedative and anticonvulsant therapy. Intubation and ventilation can be required. A sedative, antianxiety, and anticonvulsant treatment with benzodiazepines is usually indicated. Seizures can be treated with benzodiazepines or barbiturates. Arterial hypertension can be treated with urapidil, clonidine, nitroprusside, nitrates, or labetalol; beta-blockers alone without alpha-blockade should be avoided. The spectrum of cardiovascular complications and side effects is similar to cocaine stimulants (myocardial vasoconstriction, increased oxygen demand with a fixed or limited myocardial oxygen supply, and increased platelet aggregation propensity). Dantrolene is also recommended for hyperthermia, if temperature is >39 °C after initial treatment. It was considered probably safe and effective. The association with malignant hyperthermia is controversial. Clomethiazole or diazepam was effective in animal experiments for hyperthermia. Antipsychotic drugs are contraindicated as they might lower the seizure threshold, and it is difficult to differentiate the clinical presentation from the neuroleptic malignant syndrome. Hyponatremia should be carefully corrected. Metabolic acidosis should be corrected (especially when the QT interval is prolonged). In case of organ failure, conventional supportive ICU therapy is provided. Especially dangerous is the concomitant use of tricyclic antidepressants and monoamine oxidase inhibitors with MDMA.

Excessive release of serotonin leads to cerebral seizures, tremors, loss of consciousness, ventricular fibrillation, and death (Steadman and Birnbach 2003; Hernandez et al. 2005; Hall and Henry 2006; Grunau et al. 2010).

111.6.3 Elective Procedure

If patients undergo procedures in the drug-free interval, a careful evaluation is necessary as outlined above. A history of seizures, a decreased hepatic and renal function, and coagulation disorder infections are of interest in all patients. All anesthetics should be titrated according to the effect (Kork et al. 2010). PCP and LSD might prolong succinylcholine via inhibition of plasma cholinesterase (Hernandez et al. 2005). Patients with MDMA-induced hyperthermia in the history should undergo a trigger-free anesthesia (Hernandez et al. 2005; Hall and Henry 2006; Steadman and Birnbach 2003). A brief intervention addressing risky use should be delivered. An interdisciplinary psychosocial counseling and treatment plan should be initiated early (Kork et al. 2010).

111.7 Cannabis

The risk profile of cannabis, also used in a dependent way, is predominantly characterized by an increased pulmonary morbidity due to smoking. During intoxication it has some dose-dependent effect on the sympathetic activity; an increase is followed by a decrease, thus tachycardia or hypotension and bradycardia. Components of cannabis might have relevant antiemetic, analgesic, anticonvulsant, and appetite increasing effects (Hernandez et al. 2005).

111.8 GABAergic Substances

Gamma-hydroxybutyrate is abused increasingly. The effect is dose dependent, may be influenced by consuming other drugs, and ranges from euphoric-relaxing effect to drowsiness and deep sleep with subsequent coma and possible respiratory depression. Side effects – nausea, vomiting, hypotension, respiratory distress, confusion, myocloni, and convulsions – were observed. It is used as K.O. drops or as a growth hormone releaser among bodybuilders. After intake it can cause a pronounced amnesia. It is not detected by routine drug screening (Steadman and Birnbach 2003; Hernandez et al. 2005). Many patients are dependent from benzodiazepines or are using them to cope with symptoms of withdrawal or comorbidity. Relevant interactions on the pharmacodynamic and pharmacokinetic level have to be considered. In these patients, an altered GABA receptor function can be assumed. All anesthetics should be titrated to the desired effect. Neuromonitoring is recommended to avoid intraoperative awareness. Abrupt withdrawal causes anxiety and may cause seizures and should be avoided. Also hypnotics are misused

and have been linked to dependency. Not only healthcare providers have misused propofol in a risky or dependent way. In short-acting hypnotics, the range between the desired effect and relevant respiratory depression is narrow, especially in combination with other substances (Steadman and Birnbach 2003; Hernandez et al. 2005; Tan et al. 2011; Lader 2011).

111.9 Conclusion

Dependent patients with SUD can safely undergo procedures under anesthesia. In general, SUD and related complications can be successfully treated. By secondary or tertiary preventive measures in a multimodal interdisciplinary concept, the increased risk can be significantly reduced.

Elements are:

- Systematic screening, using questionnaires/markers
- Systematic diagnostic evaluation
- Brief interventions, tailored advice, and information
- Patient-centered communication style
- Individually tailored anesthesia
- Detoxification
- Abstinence
- Rehabilitation
- Psychosocial therapy
- Stepped care
- Harm reduction
- Monitoring and prevention of withdrawal symptoms, substitution therapy
- Monitoring and prevention of complications, goal-oriented therapy, symptom control, prevention of secondary injury, and stress reduction
- Complex interdisciplinary treatment strategies
- Teaching and training

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Neurobiology of Chronic Pain and Opioid Analgesic Dependence and Addiction

112

Kelly S. Barth and Jeffrey J. Borckardt

Contents

Abstract

Pain is a highly prevalent worldwide issue, affecting 20 % of all adults. With increasing use of opioid analgesics over the past decade, there has been a concomitant rise in opioid analgesic abuse and dependence, particularly in the United States, Australia, and New Zealand. Many frontline clinicians receive little, if any, training or education in pain management or opioid analgesic pharmacology. In an effort to address this educational gap, the purpose of this chapter is to provide a basic and broad overview of (1) the neurobiology of pain (including classification and pathophysiology of acute and persistent pain), (2) the processes that occur naturally and pathologically when opioid analgesics are used for pain (including analgesia, tolerance, physical dependence, and addiction), and (3) an overview of the neurobiology specific to opioid analgesic addiction. The goal of this chapter is to improve the basic understanding of pain and opioid analgesic addiction for frontline clinicians.

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112.1 Introduction

Pain is an enormous worldwide problem. Twenty percent of adults in the world suffer from pain and 10 % of adults are newly diagnosed with chronic pain each year (Goldberg and McGee 2011).

Though controversial, opioid analgesics are often prescribed for pain. In 2009, the estimated worldwide prevalence of current opioid use was between 0.5 % and 0.8 %, approximating 24–35 million people, including nearly 18 million people (5.9 % of the population) in the United States (United Nations Office on Drugs and Crime 2011).

Although not a uniquely American issue, US citizens, constituting less than 5 % of the world's population, have been consuming 80 % of the global opioid supply, including 99 % of the global hydrocodone supply (Manchikanti and Singh 2008). This places opioid analgesics as the most commonly prescribed medication of any category in the United States (Kuehn 2007). In Australia, there was a 60 % increase in prescriptions for opioid analgesics and a 180 % increase prescriptions for oxycodone from 2002 to 2009 (Hollingworth et al. 2013; United Nations Office on Drugs and Crime 2011). In New Zealand, pharmaceutical opioids diverted from the medical system have been known to be a central source of opioids for injecting drug users since the regular supply of heroin was disrupted in the 1970s (Wilkins et al. 2011).

With regard to opioid abuse and addiction, this too is a global problem, with between 13 and 22 million people worldwide abusing opioids in the past year (United Nations Office on Drugs and Crime 2011). However, when we separate opioid abuse into heroin and opioid analgesic abuse, we again see substantial regional differences. In the majority of Europe, Africa, and Asia, heroin remains the most prevalent illegally consumed opioid. In the Americas, Australia, and New Zealand, illegally diverted or misused prescription opioids (e.g., codeine, hydrocodone, morphine, hydromorphone, oxycodone, meperidine, tramadol) are the primary opioids of abuse. In 2009, 1.9 million people in the United States were addicted to prescription opioid pain relievers and 359,000 addicted to heroin (United Nations Office on Drugs and Crime 2011). Morphine and methadone have become the "street" opioids of choice in New Zealand, with the number of opioid substitution treatment centers increasing from 650 in 1990 to more than 4,000 in 2011 – despite the shortage of heroin (Robinson et al. 2011). Additionally, some African and Asian nations have also reported a surge in opioid analgesic abuse in the last decade (United Nations Office on Drugs and Crime 2011; van den Brink and Haasen 2006).

In contrast to other commonly abused substances, prescription opioids are unique in that their consumption is prescribed and endorsed by healthcare professionals. Because of this, some individuals develop a false sense of safety regarding prescription opioids and erroneously believe that the severity and risk of negative side effects is lower with prescription opioids as compared to other substances. Nonmedical prescription opioid use, however, is associated with increased rates of unintentional overdose, significant physical and mental

health problems, and staggering societal cost (e.g., emergency room admissions, lost productivity) (McLellan and Turner 2008).

The purpose of this chapter is to provide a broad overview of the basic neurobiology of pain, the processes that occur naturally and pathologically when opioid analgesics are used for pain, and neurobiology specific to opioid analgesic addiction.

112.2 Neurobiology of Pain and Opioid Addiction

112.2.1 Pain

Pain can be defined as an unpleasant sensation which is localized to a part of the body. Because pain is universally understood as a signal of disease, it is the most common symptom that brings a patient to a physician's attention. The function of the pain sensory system is to detect, localize, and identify tissue-damaging processes. Whether characterized as a symptom, sign, or syndrome, the common denominator of pain is suffering. In this regard, pain is both sensation and emotion. Pain of moderate or higher intensity is often accompanied by anxiety and an urge to escape or end the feeling. When acute, pain can be associated with behavioral arousal and a stress response consisting of increased blood pressure, heart rate, pupil diameter, and plasma cortisol levels. Additionally, local muscle contraction is often present.

112.2.1.1 Types of Pain

Pain is often initially categorized as being nociceptive or neuropathic (Portenoy 1989). Nociceptive pain is perceived by a highly specialized subset of nerve fibers (nociceptors) that respond only to painful or noxious stimuli or stimuli that become painful if prolonged. These fibers are present in nerves to the skin and deep somatic and visceral structures. The most painful stimuli activate a variety of nociceptor types in the affected area, which are summed into one nociceptive input, and ultimately lead to the subjective sense of pain.

Nociceptive Pain

Nociceptive pain is generally caused by tissue damage (e.g., injury, surgery) and can be further divided into somatic and visceral pain. Somatic pain, caused by injury to body tissues, is well localized but variable in description and experience. Visceral pain, caused by injury to internal organs, is mediated by stretch receptors and generally characterized as poorly localized, deep, dull, and cramping (e.g., pain associated with pancreatitis, cholecystitis, or nephrolithiasis).

Nociceptive pain can also be divided into musculoskeletal pain, inflammatory pain (e.g., inflammatory arthritis, postoperative pain, tissue injury, infection), or mechanical/compressive pain (e.g., low back pain, neck pain, visceral pain from expanding tumor masses).

Neuropathic Pain

Neuropathic pain is caused by abnormal neural activity due to disease, injury, or dysfunction of the nervous system. It generally persists without ongoing disease (e.g., diabetic neuropathy, trigeminal neuralgia, or thalamic pain syndrome). Depending on which type of neural injury and the location of the neural injury, neuropathic pain can be further subdivided into peripheral neuropathy, sympathetically mediated pain, and central pain.

Peripheral neuropathy is caused by damage to a peripheral nerve (without associated autonomic change, e.g., postherpetic neuralgia and neuroma formation). Sympathetically mediated pain arises from injury to a peripheral nerve which does have associated autonomic changes (e.g., complex regional pain syndrome, causalgia). Central pain arises from abnormal central nervous system activity (e.g., phantom limb pain, pain from spinal cord injuries, and poststroke pain).

Mononeuropathy affects only one nerve; mononeuropathy multiplex affects several nerves in different areas of the body; and polyneuropathy describes diffuse and bilateral neuropathy.

112.2.1.2 Pathogenesis of Pain

Acute Pain

Any pain sensation begins with a noxious stimulus sensed by peripheral nociceptors. A-delta fibers are relatively fast-conducting myelinated nociceptors. They respond to thermal and mechanical stimuli and are responsible for the first (immediate) sharp pain. Unmyelinated C-fibers make up most of the peripheral nociceptors. These slow-conducting fibers respond to thermal, mechanical, and chemical stimuli, recover from fatigue more slowly than the A-delta nociceptors, and mediate delayed or longer-lasting pain, typically characterized as dull.

The pain signal is transmitted from the peripheral A-delta and C-fibers to the dorsal horn of the spinal column via primary afferent neurons. The primary ascending pathway for pain from the dorsal horn of the spinal column to the brain is the spinothalamic tract, which projects contralaterally within the spinal cord and synapses in the thalamus. Neurons from the thalamus then project to multiple brain areas in the primary and secondary somatosensory cortex, cingulate cortex, prefrontal cortex, insular cortex, amygdala, and the cerebellum. It is important to note that the spinothalamic tract axons also connect to thalamic and cortical regions linked to emotional responses, such as the cingulate gyrus and frontal lobe. This pathway is thought to mediate the unpleasant emotional aspect of pain.

In addition to ascending pain pathways, descending inhibitory and facilitatory pathways exist that modulate the experience and sensation of pain. For example, circuits from the prefrontal cortex and anterior cingulate cortex may decrease nociceptive input, indirectly augmenting analgesia. These descending fibers may also interact with the opioid system, noradrenergic system, and serotonergic system and can significantly inhibit responses to noxious stimuli. Descending facilitatory pain pathways are also present.

112.2.1.3 Mechanisms for Persistent Pain

Several mechanisms modulate the progression of acute pain to chronic pain. These include peripheral and central sensitization as well as other mechanisms (ectopic excitability, structural reorganization/phenotypic switch of neurons, primary sensory degeneration, and disinhibition).

Sensitization

Peripheral sensitization and central sensitization are the major causes of pain hypersensitivity after injury.

Peripheral Sensitization

When painful stimuli are intense, repeated, or prolonged, cells become damaged. These damaged cells can release their intracellular contents as well as synthesize substances including cytokines, chemokines, bradykinin, histamine, prostaglandins, and growth factors. As part of the inflammation process, leukotrienes are also engaged. These substances, among others, can directly activate the nociceptor terminal or sensitize the terminal so that it becomes hypersensitive to subsequent stimuli. These substances can also indirectly facilitate the sensitization process by recruiting other inflammatory substances and propagating the cycle. Therefore, in the presence of damaged tissue or inflammation, the threshold for activating nociceptors is lowered and the frequency becomes higher for all stimulus intensities. Additionally, in the presence of injury and inflammation, nociceptors themselves can begin to express new channels, further facilitating the sensitization process. A good example of peripheral sensitization is sunburn. The decreased threshold for activating the nociceptors in the damaged area serves to protect the area from further injury through avoidance of pain.

Central Sensitization

Central sensitization is caused by an increase in excitability of central nociceptor transmission neurons of the spinal cord (at the level of the synaptic transfer from the nociceptor terminal to dorsal horn neurons). Initially, strong nociceptive input, which may come from acute injury, chronic pain syndromes, or peripheral sensitization, activates the dorsal horn neurons and causes a massive release of glutamate and co-regulatory peptides. Glutamate, a major excitatory neurotransmitter, modulates synaptic transmission in the dorsal horn in several ways. First, glutamate binds alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropioninc acid (AMPA) receptors on dorsal horn neurons, which mediates fast excitatory transmission. Additionally, glutamate interacts with N-methyl-D-aspartic acid (NMDA) receptors. During a normal, physiologic pain transmission, the NMDA receptor is physically blocked by a magnesium ion so that no current flows if glutamate binds the receptor. Massive release of glutamate in the dorsal horn, which can occur with acute or persistent injury, not only activates AMPA receptors, facilitating fast excitatory transmission, but also causes strong membrane depolarization resulting in removal of the magnesium blockade to the NMDA receptor,

thereby increasing the time the channel is open. Additionally, the NMDA receptor is phosphorylated, which increases its distribution in the synaptic membrane and its responsiveness to glutamate. The increase in excitability of the dorsal horn cell means that it can be activated by normally subthreshold inputs, with increased response to suprathreshold inputs, leading to the process of central sensitization.

Other Mechanisms for Persistent Pain

In the face of injury, multiple changes in the functioning and structure of nociceptors and their pathways can lead to persistent pain. When sensory neurons are injured, they can become altered such that they begin to spontaneously initiate action potentials independent of a stimulus, similar to a pacemaker. These pacemaker-like action potentials are postulated to arise due to upregulation of voltage-gated sodium channels (or their subunits), upregulation of receptors in myelinated neurons, or downregulation of potassium channels on nociceptors. Additional alterations in the sensory neurons from nerve injury can lead to actual physical rearrangement and new growth in the circuitry of the dorsal horn and for normally quiescent glial cells in the spinal cord to become activated, producing cytokines and chemokines that alter patterns of gene transcription in neurons. Moreso, neuromodulators that are normally expressed only in C-fibers (like brain-derived neurotrophic factor and substance P) may begin to be expressed in large-diameter A fiber neurons.

Nerve injury can also decrease inhibitory pain pathways in the dorsal horn. Excessive glutamate release, failure of glutamate uptake, or TNF-alpha released from microglia can lead to selective apoptosis of GABAergic inhibitory synaptic currents. This loss in inhibitory GABA function can recruit previously absent A-beta fiber activity, effectively unmasking a previously silent pathway.

Pain Modulation: How Psychological Factors Can Contribute to Chronic Pain

In clinical work with patients experiencing pain, it is clear that the pain produced by similar injuries can be remarkably variable in different situations and in different people. Some patients with back injuries, for example, can have a full recovery, while others can become severely disabled with a seemingly minor injury. Furthermore, even the suggestion of relief can have a significant analgesic effect (placebo) in certain patients, whereas others can find even minor injuries (such as venipuncture) unbearable. It is known that the expectation of pain can induce pain without a noxious stimulus (anticipatory pain), whereas merely having perceived control over pain can decrease pain substantially.

The powerful effect of expectation and other psychological variables on the perceived intensity of pain implies the existence of brain circuits that can modulate the activity of the pain-transmission pathways.

Although there are probably several circuits that can modulate pain, one has been studied extensively. This circuit has links in the hypothalamus, midbrain, and medulla and selectively controls spinal pain-transmission neurons through a descending pathway. There is good evidence that this pain-modulating circuit also contributes to the pain-relieving effect of opioid analgesic medications.

Each of the component structures of the pathway contains opioid receptors and is sensitive to the direct application of opioid drugs. Furthermore, lesions to the system reduce the analgesic effect of systemically administered opioids such as morphine. Along with the opioid receptor, the component nuclei of this pain-modulating circuit contain endogenous opioid peptides such as enkephalins and **β**-endorphin.

The most reliable way to activate this endogenous opioid-mediated modulating system is by prolonged pain and/or fear. There is evidence that pain-relieving endogenous opioids are released following operative procedures and even in patients given a placebo for pain relief.

Pain modulation is bidirectional. Pain-modulating circuits not only produce analgesia but are also capable of increasing pain. Both pain-inhibiting and pain-facilitating neurons in the medulla project to and control spinal pain-transmission neurons. Since pain-transmission neurons can be activated by modulatory neurons, it is theoretically possible to generate a pain signal with no peripheral noxious stimulus. Such mechanisms could account for the finding that pain can be induced by suggestion alone and may provide a framework for understanding how psychological factors can contribute to chronic pain.

112.2.2 Neurobiology of Opioid Analgesia, Tolerance, and Dependence

Most of the commercially available opioid analgesics act at the mu (μ) opioid receptor, differing mainly in potency, speed of onset, duration of action, and optimal route of administration. Opioid agonists produce analgesia through direct action in brain and spinal cord regions involved in the transmission and modulation of pain. Additionally, some effects may be mediated by opioid receptors on peripheral sensory nerve endings.

112.2.2.1 Receptor Types

There are three major classes of opioid receptors: mu (μ), delta (**δ**), and kappa (**κ**). All are members of the G protein-coupled family of receptors. Multiple receptor subtypes have been proposed based on pharmacologic criteria, including μ1, μ2; **δ**1, **δ**2; and **κ**1, **κ**2, and **κ**3. Since an opioid may function with different potencies as an agonist, partial agonist, or antagonist at more than one receptor class or subtype, it is not surprising that these agents are capable of diverse pharmacologic effects.

112.2.2.2 Cellular Actions and Neural Mechanisms for Central and Peripheral Opioid Analgesia

At the molecular level, opioid receptors are physically coupled to G proteins. Opioid peptides have two well-established direct G protein-coupled actions on the opioid receptors of pain neurons: (1) they inhibit voltage-gated (N-type) calcium channels in the presynaptic membrane of primary sensory neurons,

thereby preventing the release of neurotransmitters, and (2) they hyperpolarize, and thus inhibit, postsynaptic secondary neurons by activating potassium channels, preventing the onset of action potentials. The presynaptic action – depressed transmitter release – has been demonstrated for a large number of neurotransmitters, including acetylcholine, norepinephrine, serotonin, substance P, and glutamate (the principal excitatory amino acid released from nociceptive nerve terminals).

Endogenous opioid peptides are the major inhibitory neurotransmitters in the dorsal horn of the spinal cord, and pharmaceutical opioids have been developed in order to mimic this action in order to provide pain relief. The majority of currently available opioid analgesics act primarily at the μ-opioid receptor. As μ-opioid receptors are also expressed in the medullary respiratory control center, the medullary chemoreceptor zone, and the gastrointestinal tract, opioids may also produce respiratory depression, nausea, vomiting, and constipation. Therefore, both the analgesic effects of opioid analgesics and the primary side effects and physical dependence result principally from actions at μ-receptors. The primary spinal involvement of the pain-relieving aspects of opioids has been exploited clinically by direct application of opioid agonists to the spinal cord. This can provide regional analgesic effects without causing the systemic effects of respiratory depression, nausea, vomiting, and sedation that may occur from the supraspinal actions of systemically administered opioids.

It is important to note that systemic opioid analgesic effects are complex and also include interaction with **δ** and **κ** receptors, both directly and through activation of endogenous opioid peptides. For example, when opioid analgesics are given systemically, part of the pain-relieving action involves the release of endogenous opioid peptides. All three receptor subtypes (μ, **κ**, **δ**) are present in high concentrations in the dorsal horn of the spinal cord and modulate supraspinal and spinal analgesia, but each receptor subtype responds with different affinity to endogenous opioid peptides. **δ** receptors are thought to have high affinity to the endogenous opioid class of enkephalins and are also thought to modulate hormone and neurotransmitter release. **κ-**receptors have high affinity for dynorphins and are thought to be responsible for psychotomimetic effects and slowed gastrointestinal transit of exogenous opioids. An exogenous opioid agonist (e.g., morphine) may act primarily and directly at the μ-receptor, but this action may evoke the release of endogenous opioids that additionally act at **δ**- and **κ**-receptors, causing both additional pain relief and additional side effects. Thus, even a receptor-selective ligand can initiate a complex sequence of events involving multiple synapses, transmitters, and receptor types.

In an effort to develop opioid analgesics with reduced side effect profiles, especially related to respiratory depression, tolerance, and addiction, there has been development of compounds that show preference for **κ**-opioid receptors, such as butorphanol and nalbuphine. However, these agents have been limited in their clinical success as analgesics due to dysphoric reactions and limited potency. It is interesting that butorphanol has been shown to cause significantly greater analgesia in women than in men. In fact, gender-based differences in analgesia mediated by μ- and **δ**-receptor activation have been widely reported.

Partial-agonists at the μ-opioid receptor, such as buprenorphine, have also been shown to have less propensity for tolerance than full opioid agonists.

Under most circumstances, exogenous opioid analgesics are given systemically and so act simultaneously at multiple sites. These include not only the ascending pathways of pain transmission through nociceptors detailed above but also descending (modulatory) pathways. As opioids directly inhibit pain neurons, there is a simultaneous activation of descending inhibitory neurons that send processes to the spinal cord and inhibit pain neurons. This activation has been shown to result from the inhibition of inhibitory neurons in several locations. Taken together, interactions at these sites increase the overall analgesic effect of opioid agonists.

In addition to actions in the central nervous system, animal and human clinical studies have demonstrated that endogenous and exogenous opioids can produce opioid-mediated analgesia at sites outside the central nervous system. The activation of peripheral μ-receptors on sensory terminals results in a decrease in sensory neuron activity and transmitter release and inhibition of the pain signal. Endogenously, **β**-endorphins released by immune cells within injured or inflamed tissue represent one source of physiologic peripheral μ-receptor activation. Peripheral administration of exogenous opioids, for example, into the knees of patients following arthroscopic knee surgery, has shown clinical benefit up to one day after administration.

112.2.2.3 Pharmacogenetics

There is wide interindividual variability among patients in response to opioid analgesics. The majority of exogenous opioids are metabolized by the cytochrome P450 2D6 (CYP2D6) pathway or by glucuronidation. Codeine, oxycodone, and hydrocodone undergo O-methylation to produce metabolites that have a stronger μ-receptor affinity. Therefore, they exert their analgesic properties mainly through their metabolites. The O-methylation step is controlled by CYP2D6. CYP2D6 polymorphisms have been associated with altered enzyme activity that could result in altered drug effects. For example, poor metabolizers, or individuals who do not express functional CYP2D6, can only form trace amounts of O-methylated products and may experience reduced analgesia. For example, in poor metabolizers who take codeine, a prodrug that is metabolized to morphine, only trace amounts of morphine will be detected. Conversely, drugs like morphine, oxymorphone, and hydromorphone are already O-demethylated, so they will be less effected by metabolism and have smaller interindividual variability of opioid effects.

112.2.2.4 Tolerance and Dependence

With frequently repeated therapeutic or recreational doses of morphine or its surrogates, there is a gradual loss in effectiveness which requires higher doses of the substance to get the same effect; this is termed tolerance. Along with tolerance, physical dependence develops, which is defined as a characteristic withdrawal or abstinence syndrome when a drug is stopped or an antagonist is administered.

The mechanism of development of tolerance and physical dependence is not completely understood, but persistent activation of μ-receptors, such as what occurs with the treatment of severe chronic pain, appears to play a primary role in its induction and maintenance. It is also interesting to note that tolerance develops to most side effects of opioids such as euphoria, respiratory depression, and nausea, but not to the side effect of constipation.

Withdrawal (Dependence)

The locus ceruleus, located in the upper pons, is a major source of norepinephrine for the brain and an important mediator of tolerance to opioids. There are opioid receptors in the locus ceruleus, and when activated, they suppress the release of norepinephrine, contributing to the classic symptoms of opioid intoxication, including drowsiness, slowed breathing, and low blood pressure. With repeated exposure to opioids, the locus ceruleus increases alternative paths of norepinephrine production in order to maintain a homeostatic alertness. When opioids are subsequently withdrawn, there is a relative surge of norepinephrine. This leads to subjective symptoms of withdrawal, including increased anxiety and tremor, among other symptoms. This is the site of action of clonidine when given to relieve symptoms of opioid withdrawal.

Other brain areas in addition to the locus ceruleus also contribute to the production of withdrawal symptoms, including the mesolimbic reward system. For example, opioid receptors are located in the ventral tegmental area, and when tolerance develops, there is a decrease in the release of dopamine into the nucleus accumbens. In addition to becoming tolerant to the euphoric effects of the drug, this may also prevent the patient from obtaining pleasure from normally rewarding activities such as eating. These changes in the ventral tegmental area and dopamine reward systems, though not fully understood, form an important brain system underlying craving and compulsive drug use.

Tolerance

On a molecular level, chronic opioid administration results in an upregulation of the intracellular cyclic adenosine monophosphate (cAMP) system at multiple levels in the locus ceruleus. These changes include increased levels of Gi and Go proteins (alpha subunits), adenylate cyclase, and cAMP-dependent protein kinase. Given the location of these changes in the locus ceruleus, it is postulated that the upregulation of the adenylate cyclase system may play a role in the development of tolerance. It is less clear whether the specific changes in the second-messenger function in the locus ceruleus persist beyond the period of chronic opioid administration.

Although the process of upregulation of the cAMP system is associated with tolerance, more recent theories suggest it is not sufficient to explain it. Another hypothesis for the development of opioid tolerance and dependence is based on the concept of receptor recycling. Normally, activation of μ-receptors by endogenous endorphins results in endocytosis followed by resensitization and recycling of the receptor to the plasma membrane. This process is thought to be an important component of tolerance. It is known that morphine, a drug known to be susceptible

to tolerance, fails to induce endocytosis of the μ-opioid receptor, whereas methadone, which is less susceptible to tolerance and used for the treatment of chronic pain and opioid addiction, does induce receptor endocytosis. This suggests that maintenance of normal sensitivity of μ-receptors requires reactivation by endocytosis and recycling at the plasma membrane. A related hypothesis suggests that receptor uncoupling is involved with tolerance due to a dysfunction of structural interactions between the μ-receptor and G proteins, second-messenger systems, and their target ion channels. This uncoupling and recoupling of μ-receptor function is likely linked to receptor recycling.

Another interesting theory involves the NMDA-receptor ion channel complex, which has been shown to play a central role in the development and maintenance of tolerance in that NMDA-receptor antagonists such as ketamine can block tolerance development. Although a role in endocytosis is not yet clearly defined, the development of novel NMDA-receptor antagonists or other strategies to recouple μ-receptors to their target ion channels provides hope for achieving a clinically effective means to prevent or reverse opioid analgesic tolerance. One last hypothesis suggests that the **δ**-opioid receptor is involved with tolerance and functions as an independent component in the maintenance of tolerance.

In addition to the development of tolerance, persistent administration of opioid analgesics has been observed to increase the sensation of pain leading to a state of hyperalgesia. This phenomenon has been observed with several opioid analgesics, including morphine, fentanyl, and remifentanil. Spinal dynorphin and activation of the bradykinin receptor have emerged as important candidates for the mediation of opioid-induced hyperalgesia.

112.2.3 Neurobiology of Opioid Addiction

The pleasure derived when opioids activate the brain's natural reward system promotes continued drug use during the initial stages of opioid addiction. Subsequently, repeated exposure to opioid drugs induces the brain mechanisms of dependence, which leads to daily drug use to avert the unpleasant symptoms of drug withdrawal. Further prolonged use produces more long-lasting changes in the brain that may underlie the compulsive drug-seeking behavior and related adverse consequences that are the hallmarks of addiction. Drug addiction is characterized by a pathological motivation for drug-seeking and drug-use behaviors that is associated with the inability to stop such behaviors, even despite negative consequences related to drug use (Kalivas and Volkow 2005). Recent scientific research has generated several models to explain how habitual drug use produces changes in the brain that may lead to drug addiction. In reality, the process of addiction probably involves components from each of these models, as well as other features.

The general neurobiology of addiction has been detailed in previous chapters of this text. To understand the neurobiology of addiction specific to opioids and prescription opioids, we will review animal models that most closely mimic "drug-seeking behavior" (drug reinforcement studies) and relapse and

reinstatement (conditioning homeostatic models), involving opioids. We will also review more recent literature describing structural brain changes associated with prescription opioid use and dependence.

112.2.3.1 Behavioral Neurobiology of Opioid Reinforcement ("Drug-Seeking Behavior")

Opioid tolerance, dependence, and addiction are all manifestations of brain changes resulting from chronic opioid use and abuse. It is known, however, that one does not have to be physically dependent upon opioids to experience primary reinforcing properties of opioids. Decades ago, Bozarth and Wise (1984) demonstrated the neurobiology of this phenomenon in a study on drug-naive rats that learned to press a lever in order to receive direct injections of morphine into the ventral tegmental area (mimicking drug-seeking behavior in humans). The rats were then exposed to a challenge with naloxone (a direct opioid antagonist), which did not precipitate signs of withdrawal following the morphine injections. Moreover, signs of withdrawal were not seen after long-term morphine infusion into the ventral tegmental area but were observed after chronic infusion into the periventricular gray region. The data strongly suggested that the pathways mediating opioid reinforcement (e.g., the ventral tegmental area) were independent of pathways mediating the signs of opioid withdrawal (e.g., the locus ceruleus).

The pathways for opioid reinforcement and dependence, however, are clearly overlapped in some areas of the brain where opioids can act as both reinforcers and cause dependence. In the nucleus accumbens, a brain area important for reward and pleasure, and in the locus ceruleus, an area of the pons associated with physiologic response to stress and panic (and producer of norepinephrine), opioids can acts as reinforcers. But studies have also shown that with direct placement of naloxone in the nucleus accumbens of morphine-dependent rats, withdrawal can cause the disruption of food-mediated behaviors and conditioned place aversion. The locus ceruleus is also sensitive to the acute reinforcing effects of opioids (resulting in a suppression of locus ceruleus activity), as well as to the effects of opioid withdrawal (as characterized by a large increase in locus ceruleus activity). Thus, it is clear that some neurons are affected both by the acute reinforcing effects of opioids as well as by opioid withdrawal. The data are consistent with the view that although opioids will serve as reinforcers in the absence of physical dependence, the "motivation" for opioid self-administration is enhanced during opioid withdrawal.

As with other drugs of abuse, there is evidence that opioid reinforcement involves activation of dopamine neurons, with an increase in extracellular dopamine concentrations in the nucleus accumbens. With repeated administration, more opioid is needed to stimulate the ventral tegmental area brain cells of the mesolimbic reward system to release the same amount of dopamine in the nucleus accumbens. Therefore, more opioid is needed to produce pleasure comparable to that provided in previous drug-taking episodes. Interestingly, although the lesioning of dopamine neurons in the nucleus accumbens eliminates stimulant self-administration, it fails to eliminate opioid self-administration in rats (Koob and Bloom 1988). Opioids may also indirectly increase the firing of

dopamine neurons by activating μ-opioid receptors in the ventral tegmental area and nucleus accumbens, producing local disinhibitory effects on the dopamine neurons. Not surprisingly, naloxone blocks the effects of opioids on the ventral tegmental area (Britt and Wise 1983).

It is interesting to note that with chronic administration of opioids, an increased sensitization to their reinforcing properties (reverse tolerance) can be seen. It is hypothesized that chronic opioid administration can affect gene expression of guanine-nucleotide binding proteins (G proteins) and the cyclic adenosine monophosphate (cAMP) system. These changes in the molecular biology of second-messenger function may be related to the development of sensitization to the reinforcing properties of opioids.

112.2.3.2 Models for Progression to Addiction

Theories on the neurobiologic basis of addiction are not unique to opioid addiction and have been reviewed in previous chapters. We will provide a brief review of the neurobiologic theories of addiction as they apply to opioid and prescription opioid addiction.

112.2.3.3 The "Changed Set-Point" Model in Relation to Prescription Opioid Dependence

The "changed set-point" model of drug addiction postulates that drug abuse alters a biological or physiological setting or baseline of the dopamine reward system. This model has several variants based on the altered neurobiology of the dopamine neurons in the ventral tegmental area, the nucleus accumbens, and the locus ceruleus during the early phases of withdrawal and abstinence. One variant of the changed set-point model, by Koob and LeMoal (2001), is based on the idea that neurons of the mesolimbic reward pathways are naturally "set" to release enough dopamine in the nucleus accumbens to produce a normal level of pleasure. Koob and LeMoal suggest that repeated doses of opioids initiate a vicious cycle of changing this set point which results in decreased release of dopamine during normally pleasurable activities (in the absence of opioids).

112.2.3.4 Molecular, Genetic, and Structural Changes with Acute and Chronic Opioid Exposure

On a molecular level, it is known that the dopamine receptor, which uses cAMP as its second messenger, is affected by chronic morphine administration (Beitner-Johnson and Guitart 1992). Chronic morphine treatment results in decreased levels of the G protein that inhibits adenylate cyclase, with increases in adenylate cyclase and cAMP-dependent protein kinase. Ultimately, these changes can alter the structural features of mesolimbic dopamine neurons so as to reduce the ability of these cells to transmit dopamine signals to postsynaptic cells in the nucleus accumbens. This leads to an effective resetting of the set point of the mesolimbic dopamine neurons.

Chronic morphine treatment also results in a decrease in the phosphorylation state of tyrosine hydroxylase in the nucleus accumbens (the rate-limiting enzyme in

the synthesis of dopamine) (Bietner-Johnson and Guitart 1992). This results in decreased functional activity of the enzyme in the nucleus accumbens, whereas there is upregulation (and increased phosphorylation) of the enzyme in the ventral tegmental area.

Bronstein and colleagues (1990) have reported that there is a decline in pro-opiomelanocortin (POMC) messenger ribonucleic acid (mRNA) levels with chronic morphine treatment. Because POMC yields several biologically active peptides, including **β**-endorphin, ACTH, melanocyte-stimulating hormone, and B-lipotropin, morphine may also affect the biosynthesis of the endogenous opioid, **β**-endorphin. Specifically, the authors report that chronic morphine treatment appears to result in the preferential production of **β**-endorphin 1–27 (which functions as an antagonist at the μ-opioid receptor) relative to **β**-endorphin 1–31 (which functions as an agonist at the μ-receptor). Acute stress also favors the production of **β**-endorphin 1–27 relative to **β**-endorphin 1–31. Chronic treatment with naltrexone (a narcotic antagonist) increases the mRNA for POMC and results in an increase in **β**-endorphin 1–27. The work suggests that the POMC system is quite sensitive to the effects of exogenous opioids as well as to acute stress.

Chronic opioid treatment also produces regionally specific changes in gene expression of a number of second-messenger functions in the brain that are associated with the reinforcing effects of opioids (Beitner-Johnson and Guitart 1992). Taken together, these changes result in decreased dopamine synthesis in the nucleus accumbens and changes in dopamine receptor function.

Structurally, chronic morphine treatment results in a decrease in neurofilament proteins in dopamine neurons in the ventral tegmental area. These effects are regionally specific. The neurofilament proteins form a major component of the cytoskeleton. Consistent with this result, cytoskeletal or cytoskeletal-associated elements of dopamine neurons have been shown to be altered by chronic morphine treatment resulting in selective reduction in the size of ventral tegmental area dopamine neurons (Beitner-Johnson and Guitart 1992).

As described previously, a changed set point also occurs in the locus ceruleus, but in the opposite direction, such that norepinephrine release is increased during withdrawal. Under this changed set-point model, both the positive (drug liking) and negative (drug withdrawal) aspects of drug addiction are accounted for.

It remains to be seen whether specific changes in second-messenger function in locus ceruleus (associated with tolerance and dependence) and the mesolimbic dopamine system persist beyond the period of chronic opioid administration to account for some of the signs and symptoms of protracted withdrawal/abstinence.

In 2000, researchers further specified the changed set-point model in describing additional specific ways that dopamine neurons can become dysfunctional in the face of repeated opioid exposure (Grace 2000). They postulate that the resting level of dopamine released into the nucleus accumbens is the result of two factors: cortical excitatory (glutamate) neurons that drive the dopamine neurons of the ventral tegmental area to release dopamine and autoreceptors (“brakes”) that shut down further release when dopamine concentrations become excessive.

Activation of opioid receptors by heroin and prescription opioids initially bypasses these brakes and leads to a large release of dopamine in the nucleus accumbens. With repeated use and further surges of dopamine in the reward system, the brain responds by increasing the number and strength of the autoreceptors ("brakes") on the dopaminergic neurons of the ventral tegmental area. In the absence of opioid administration, the enhanced autoreceptors lower the resting tone of dopamine in the reward system. This can trigger the dependent addict to take even more opioid to offset this lower resting tone of dopamine. Whenever he or she stops using opioids, a state of relative dopamine deficiency will result, manifesting in opioid withdrawal symptoms such as dysphoria, agitation, body pain, and malaise. This places the individual at high risk for relapse to drug use.

Thus, several mechanisms in the locus ceruleus, ventral tegmental area, and nucleus accumbens pathways are likely operating during addiction and relapse. Additionally, overactive cortical excitatory brain pathways caused by opioid addiction may also contribute to the changed set-point model, in that excitatory cortical projections may produce little activation in the ventral tegmental area during the resting state, leading to additional reductions in dopamine. However, when the addicted individual is exposed to cues that produce craving, the excitatory (glutamate) pathways may get sufficiently active to raise dopamine and stimulate desire for a greater high. This same increase in glutamate activity will raise norepinephrine release from the locus ceruleus to produce a dysphoric state during withdrawal predisposing to relapse and continued addiction.

112.2.3.5 Cognitive Deficits Model

The cognitive deficits model of drug addiction proposes that individuals who develop addictive disorders have abnormalities in the prefrontal cortex, an area important for judgment, planning, and other executive functions. The prefrontal cortex sends inhibitory signals to the dopamine neurons of the ventral tegmental area of the mesolimbic reward system and enables individuals to delay immediate gratification for the sake of longer-term goals. This model proposes that those with addictive disorders have defects in the ability of the prefrontal cortex to inhibit the mesolimbic reward system, and as a result, they have decreased ability to use higher-level judgment or restrain impulses to use drugs.

Supporting this concept, it has been shown that stimulant drugs, such as methamphetamine, can damage a specific brain circuit – the frontostriatal loop – that carries inhibitory (GABA) signals from the prefrontal cortex to the mesolimbic reward system. In contrast, heroin has been shown to damage the prefrontal cortex but not the frontostriatal loop. It may be that individuals predisposed to opioid addiction have some degree of prefrontal damage that is independent of their opioid abuse, either inherited genetically or caused by some other factor or event in their lives (Kosten 1998). Finally, the cognitive deficits model of addiction could explain the clinical finding that heroin addiction tends to be more severe in those with comorbid antisocial personality disorder – a condition that is independently associated with deficits in the prefrontal cortex (Raine et al. 2000).

112.2.3.6 Animal and Human Studies on Brain Changes Associated with Chronic Opioid Analgesic Administration

Chronic opioid exposure is known to produce neuroplastic changes in animals. However, despite theories based on animal models and literature extrapolated from research on heroin addicts, very little direct research has been done evaluating individuals with primary prescription opioid addiction. Additionally, there has been little differentiation in human data between opioid-dependent individuals and nonaddicted users of chronic prescription opioids for pain, two very different clinical populations.

In a recent small cross-sectional study of ten prescription opioid-dependent individuals and 10 age-matched controls, researchers found that the prescription opioid-dependent subjects demonstrated decreased gray matter volume in the bilateral amygdalae (Upadhyay et al. 2010). The amygdala is a key reward-modulating structure that is known to underlie opioid-related addiction, dependence, and tolerance. Morphologic abnormalities in the amygdalae of the prescription opioid-dependent individuals may explain an additional possible deficiency in the neural reward-processing network. The results of this study added to existing animal literature that showed that opioid exposure can have a broad range of effects on the amygdala, including decreased μ-opioid receptor sensitivity (Maher et al. 2005), modulated gamma-aminobutyric acid (GABA) receptor functioning (Zarrindast et al. 2004), and modified glutamate receptor targeting (Glass et al. 2005).

A subsequent pilot study (Younger et al. 2011) was the first longitudinal study to investigate prescription opioid effects on the human brain. In this study, ten nonaddicted opioid-naive individuals with chronic low back pain received structural brain MRIs before and after 1 month of daily morphine analgesic therapy. After 1 month of morphine, the investigators found significant volumetric decreases in the right amygdala and significant volumetric increases in the right hypothalamus, left inferior frontal gyrus, right caudal pons, and right ventral posterior cingulate. These changes persisted on average for 5 months after cessation of opioids. The same scanning procedure was also completed on nine patients with low back pain receiving a blinded placebo substance, and no morphologic changes were found. This study adds to a growing body of evidence that opioid exposure can cause structural and functional derangements in reward- and affect-processing circuitry and suggests that these changes can occur over a short amount of time in humans exposed to prescription opioids. Further research is needed to determine the clinical significance of this as it related to both nonaddicted and addicted individuals.

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Cognitive-Behavioural and Other Psychosocial Approaches for Patients with Chronic Pain and Substance Abuse Problems

113

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Contents

Abstract

Managing chronic pain is challenging and further complicated in patients with substance abuse problems. There is growing evidence supporting the efficacy of psychological approaches to pain management. In most cases, psychological approaches for pain management are applied as an adjunct to medication management for pain. For patients with pain and substance abuse problems,

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psychological strategies for pain management may serve a more central role. Despite efficacious psychosocial pain management interventions and advancing medication management for pain, there is evidence that chronic pain cannot be adequately managed and may progress in the context of substance abuse problems. For this reason, the care of patients with chronic pain and substance abuse problems must be carefully coordinated to meet the multiple needs of the patient. Pain management in the context of substance abuse problems may be best conceptualized within the biopsychosocial model of pain. The biopsychosocial model of pain emphasizes that pain is a biological, psychological, and social experience. Within this model, pain management is approached by simultaneously addressing pain through biological, psychological, and social mechanisms. Several psychosocial approaches to pain management have been developed, tested, and shown efficacious for reducing pain, pain-related disability, and psychological distress. In this chapter, we present information on pain management in patients with chronic pain and substance abuse problems from a biopsychosocial perspective, emphasizing work in psychosocial pain management strategies, behavioral strategies for substance abuse problems, and possible strategies for integrating the two.

113.1 Introduction

Managing chronic pain is challenging and further complicated in patients with substance abuse problems. There is growing evidence supporting the efficacy of psychological approaches to pain management (Williams et al. 2012). In most cases, psychological approaches for pain management are applied as an adjunct to medication management for pain. For patients with pain and substance abuse problems, psychological strategies for pain management may serve a more central role. Despite efficacious psychosocial pain management interventions and advancing medication management for pain, there is evidence that chronic pain cannot be adequately managed and may progress in the context of substance abuse problems (Savage 1993, 1996; Manchikanti et al. 2008). For this reason, the care of patients with chronic pain and substance abuse problems must be carefully coordinated to meet the multiple needs of the patient.

The management of pain in the context of substance abuse problems may be best conceptualized within the biopsychosocial model of pain. The biopsychosocial model of pain emphasizes that pain is a biological, psychological, and social experience (Keefe and France 1999; Engel 1977, 1980). Within this model, pain management is approached by simultaneously addressing pain through biological (e.g., rehabilitation, pharmacotherapy), psychological (e.g., behaviors, cognitions, affect), and social (e.g., relationships, recreation) mechanisms. The biopsychosocial model is in contrast to the biomedical model, which has the objective of explaining and eliminating pain by addressing the anatomical or pathological causes of pain.

Several psychosocial approaches to pain management have been developed, tested, and shown efficacious for reducing pain, pain-related disability, and psychological distress. In this chapter, we present information on pain management in patients with chronic pain and substance abuse problems from a biopsychosocial perspective, emphasizing work in psychosocial pain management strategies, behavioral strategies for substance abuse problems, and possible strategies for integrating the two.

113.2 Managing Pain in Patients with Substance Abuse Problems

Chronic pain is prevalent and its management can be complicated. Managing chronic pain in patients with substance abuse problems presents an even greater treatment challenge.

113.2.1 Concerns of Pain Medications

The standard of care for treating patients with chronic non-cancer-related pain is opioid medications (Portenoy 2000; Ballantyne and Mao 2003). There is empirical evidence supporting the use of opioid medication for chronic pain, and several organizations provide statements and directions for providers to follow when prescribing opioid medication for chronic pain (Manchikanti et al. 2012; Chou 2009; Chou et al. 2009; Dale et al. 2011). However, even in patients who do not have a history of substance abuse problems, there is often reluctance by many medical providers to supply long-term opioid medication due to concerns of addiction, as well as respiratory depression and decreased pain tolerance (Passik 2009). These concerns are greater in patients with a known history of substance abuse problems or patients who may be at risk for substance abuse problems.

113.2.2 Risk Factors for Substance Abuse Problems

While the actual risk for opioid addiction may be lower than perceived by both medical providers and patients, it is important to be aware of patients with chronic pain who may be at an increased risk for substance abuse problems. Risk factors have been identified that may indicate a patient with chronic pain could be vulnerable to substance abuse problems. Passik (2009) identified several factors that are listed in Table 113.1. The behaviors indentified in Table 113.1 are important for providers to keep in mind and monitor during treatment.

In addition to observable behaviors at the time of treatment, there are a number of past behaviors, patient beliefs, and emotional difficulties that can contribute to an increased risk of substance abuse problems in patients with chronic pain. A prior history of substance abuse is the most consistent predictor of medication abuse in

Table 113.1 Factors that may be related to substance abuse problems in patients with chronic pain

1.	Use of alcohol or illicit drugs
2.	Problems functioning at work or in other social roles
3.	Injecting oral medications
4.	Repeated dose increases
5.	Nonadherence to medication regimens or medical procedures
6.	Obtaining prescription drugs from nonmedical services
7.	Resistance to changes in prescription despite negative effects
8.	Repeated seeking of prescriptions from several medical sources
9.	Selling prescription drugs
10.	Stealing, borrowing, or losing drugs

persons with chronic pain (Ives et al. 2006; Portenoy 1996; Schieffer et al. 2005; Manchikanti et al. 2003, 2006). Studies have found that patients in pain management programs with a history of past alcohol or illicit drug abuse (i.e., cocaine), past misuse of pain medications, past drug or driving under the influence convictions, legal problems related to alcohol or drugs use, or a family history of substance abuse were much more likely to have problems with opioid abuse and/or urine toxicology screens that were positive for misuse of opioid medications and/or illegal drug use (Ives et al. 2006; Michna et al. 2004). One study examined differences in opioid treatments in patients with chronic pain who had a history of alcohol abuse alone versus patients who had a history of poly substance abuse or oxycodone abuse. This study found that patients with only an alcohol abuse history were successfully managed on chronic opioid treatment, but that patients with a history of poly substance or oxycodone abuse were not successful candidates for long-term opioid treatment (Dunbar and Katz 1996).

Patients' beliefs about pain medication may also contribute to their use or abuse of medication for chronic pain. In a study of 288 patients with chronic pain, patients who endorsed beliefs that narcotic mediations are effective for pain control, that medications will help with their emotions, that they would be better able to function with access to free medications, and that they needed higher amounts of narcotics to experience pain relief than other patients were more likely to abuse medications for chronic pain (Schieffer et al. 2005). Interestingly, these investigators found that patients who held these beliefs and had a substance abuse history were more vulnerable to misuse of pain medication than patients who did not hold these beliefs but still had a substance abuse history.

Current or past emotional difficulties, such as depression and anxiety disorders, have been related to problems with pain medication misuse in patients having chronic pain. A history of major depressive disorder is associated with increased opioid abuse in patients with chronic pain (Manchikanti et al. 2006; Kouyanou et al. 1997; Webster and Webster 2005). Other work has found that patients with high levels of trait

anxiety, panic attacks, or post-traumatic stress disorder were more likely to have problems abusing pain medications than patients without these problems (Wilsey et al. 2008).

The relationship between emotional difficulties and pain medication misuse is likely due to several factors. Some work has found that opioid medications are not as effective in reducing pain in patients with a history of mood or anxiety disorders (Wasan et al. 2005). Given this, patients with these disorders may experience less pain relief when taking opioid medications and thus may increase their dose or use other maladaptive strategies to control their pain. Other data has found that adults who were feeling depressed or anxious were twice as likely to initiate the use of pain medications without a prescription or to use pain medications in a way other than prescribed when compared to patients who were not experiencing these symptoms (Substance Abuse and Mental Health Services Administration 2006).

Capitalizing on the multifaceted approach of the biopsychosocial model to pain management in patients with substance abuse problems may provide particularly important guidance. In the next several pages, we present information on psychological interventions for pain management that have empirical evidence to support their benefits for reducing pain, pain disability, and distress in patients with chronic pain. We focus on cognitive-behavioral approaches that have garnered the most empirical support and are most widely applied. Given the high incidence of overlap between chronic pain and substance abuse problems, we suggest that the risk factors mentioned above be assessed (i.e., through patient medical record review or patient and family self-report) at the onset of psychosocial interventions for chronic pain.

113.2.3 Cognitive-Behavioral Approaches for Pain Management

Cognitive-behavioral approaches to the management of pain are arguably the most commonly applied psychological interventions for pain. Cognitive-behavioral approaches for pain management propose that individuals with pain often develop maladaptive thought patterns (e.g., pain catastrophizing) and behaviors (e.g., activity avoidance) that can contribute to increased pain and disability (Williams et al. 2012). These cognitive-behavioral interventions target teaching patients to reconceptualize their thoughts about pain and to increase behaviors that decrease pain and eliminate behaviors that contribute to higher pain. In a meta-analysis examining the use of CBT protocols applied to patients with cancer pain, 65 % of studies found that these protocols were effective in reducing pain and that the average effect size across studies was 0.23 (95 % confidence interval 0.07–0.39; $p = 0.004$) (Abernethy et al. 2006). Other meta-analyses in general pain samples have found that cognitive and behavioral interventions are beneficial (ES = 0.46) in decreasing pain and improving pain-related disability (Morley et al. 1999). Below, we present several common strategies used in CBT interventions for pain and highlight some empirical studies examining the efficacy of CBT interventions for pain.

113.2.4 Cognitive-Behavioral Therapy Interventions for Pain Management

Cognitive-behavioral therapy (CBT) for chronic pain management includes teaching patients a variety of skills and strategies for learning to manage their pain. CBT protocols for managing chronic pain may include one skill, a few skills, or a comprehensive program of skills and strategies. Common core skills of CBT protocols for pain management include relaxation strategies such as progressive muscle relaxation and imagery, activity pacing, pleasant activity planning, cognitive restructuring, problem solving, and goal setting.

Pain coping skill training (PCST) is a CBT-based pain management protocol that has been developed and tested by Keefe and colleagues (1987, 1990) in numerous patient samples with chronic pain. PCST was developed to (1) decrease maladaptive pain catastrophizing and (2) enhance patients' ability to cope with pain and pain-related disability. Below, we present example of CBT skills and strategies with a PCST framework, using the authors' experiences to provide illustrative points – particularly in relation to how PCST skills might be applicable to patients with chronic pain and substance abuse problems.

113.2.5 Relaxation Strategies

Progressive muscle relaxation (PMR) is a relaxation strategy that involves teaching patients to recognize tension they hold in their body and to routinely use relaxation to decrease the tension. Edmund Jacobson originally developed PMR in the early 1920s (Jacobson 1938), and it has since been used for a number of physical problems (Yoo et al. 2005; Sheu et al. 2003; Yu et al. 2007). In relation to pain, patients are taught to progressively tighten and relax several muscle groups throughout their body (e.g., feet, legs, shoulders) (Bernstein and Borkovec 1973). As patients are instructed to tighten and relax their muscles, it is suggested that tightening feels like tension and relaxing feels comforting. PMR is designed to help patients quickly recognize stress and tension in their body that will likely to lead to increased pain if not controlled and to use PMR strategies to relax any bodily tension. The goal of PMR is to have patients with pain monitor their tension levels as they go throughout their day and to habituate to relaxing tension rather than letting it increase.

PMR has been well received by patients participating in research studies in our laboratory, and it is a central component to efficacious PCST studies (Keefe et al. 1987, 1990). While the use of PMR strategies in substance abuse populations has not been well studied, research has suggested that PMR could affect physiological arousal after nicotine craving (Parker et al. 1978). In patients with substance abuse problems, PMR may serve as a strategy to decrease high pain or tension (e.g., physiological arousal) that may increase patients' risk of misusing substances.

113.2.6 Imagery

Imagery is another form of relaxation that encourages the patient to focus their attention on a safe and pleasant scene, away from pain. In practice, a therapist or coach will often help patients brainstorm several safe or pleasant scenes (e.g., beach, meadow, lake, grandmother's kitchen) and then ask the patient to select the scene they would like to use for the imagery practice. One strategy to help the patient improve the quality or vividness of their image is to take the patient through an exercise where they identify what they experience with each of their senses (i.e., see, hear, feel, taste, smell) in the scene they are imagining. Imagery often starts with a brief relaxation (e.g., getting comfortable, closing eyes, focusing on breathing) that leads into the patient using their senses to imagine their pleasant image. In patients with substance abuse problems and pain, imagery practice could be dually used to distract patients from pain and any desire/craving for medication or other drugs toward a more pleasant and safe scene. Research has demonstrated the efficacy of guided imagery in reducing levels of pain (Posadzki et al. 2012) and craving (Versland and Rosenberg 2007), supporting the use of this strategy with patients who have chronic pain and substance abuse problems.

113.2.7 Activity-Related Pain Coping Strategies

Two activity-related pain coping strategies are commonly applied in PCST, as well as several other CBT pain management protocols. The first is activity-rest cycling which teaches the patient to avoid overactivity that can lead to high levels of pain and fatigue (i.e., the overactivity cycle) (France and Krishnan 1988). Activity-rest cycling involves teaching patients to schedule activities throughout their day into cycles of moderate activity and limited rest. The goal of this strategy is to teach patients a way to remain active, but to not engage in activity that is likely to lead to pain and possibly prolonged rest, fatigue, and emotional distress. In patients with substance abuse problems, the activity-rest cycle could be presented as a strategy that can help them avoid medication overuse or misuse that can result when they engage in overactivity that leads to extreme pain.

Pleasant activity planning is another activity-related strategy commonly used in CBT protocols for pain management (Keefe et al. 1990; Somers et al. 2012a). Pleasant activity planning involves helping patients brainstorm a variety of activities they might enjoy, but are not currently doing or have never tried before. Patients are encouraged to brainstorm big activities such as a trip to another country, as well as small activities such as taking time to enjoy a cup of hot tea on the porch. The rationale for pleasant activity planning is that often when patients have chronic pain, they decrease their activities and are most likely to decrease activities they enjoy (vs. activities they are obligated to do such as work or childcare). Pleasant activity planning encourages patients to think about and engage in activities they might enjoy. Often pleasant activity planning can be combined

with the activity-rest cycle to help patients enjoy an activity without overdoing it and finding themselves in higher levels of pain.

For patients with substance abuse problems, they may find that as they decrease their maladaptive substance behaviors, they have more time on their hands and/or more energy. Pleasant activity planning may be very important in helping them engage in meaningful activities and avoid relapsing to problematic substance use behaviors (McHugh et al. 2010). This strategy has been a key component to efficacious CBT interventions for substance abuse (Dutra et al. 2008; Magill and Ray 2009), suggesting that pleasant activity scheduling could be used to jointly target pain and substance use problems.

113.2.8 Cognitive Restructuring

Chronic pain is a very challenging problem and patients with chronic pain may find that they engage in negative thinking about their chronic pain. Negative thoughts about pain, while understandable, have been shown to be related to much higher levels of pain, physical disability, and emotional distress (Somers et al. 2009, 2012b; Keefe et al. 2010). Importantly, patients who engage in negative thinking about their pain have been found to use higher levels of pain medications and/or be less adherent to using their medications as prescribed. Pain catastrophizing is a negative cognition about pain that has been widely studied and appears to result in increased pain levels as well as other negative pain-related outcomes (Keefe et al. 2004). Pain catastrophizing refers to an individual's tendency to focus on and magnify pain sensations and feel helpless when they experience pain (Sullivan et al. 2001). Cognitive restructuring within the context of pain management is a strategy that helps patients begin to notice their negative thinking patterns (e.g., I will always be in pain; there is nothing I can do to help with this pain) and to replace their negative thinking with more neutral (and at times, more positive) thinking. Helping patients change their negative pain-related thoughts can increase their ability to manage their pain. Newer CBT protocols have focused their efforts on decreasing pain catastrophizing in patients with chronic pain (Riddle et al. 2012).

Cognitive restructuring may be a particularly important skill for patients with pain and substance abuse problems (Steigerwald and Stone 1999). CBT with a focus on cognitive restructuring has been shown to be effective for patients with substance abuse problems and other comorbidities (i.e., post-traumatic stress disorder) (McGovern et al. 2009). Patients with chronic pain and substance abuse problems are likely to hold a number of negative thoughts or faulty cognitions (e.g., I need this much medication because I have pain; I don't have a problem with substance use, and I can control it; there is no other option to control my pain than to misuse this substance) around their substance use and abuse. Cognitive restructuring can help patients with substance abuse problems to recognize thoughts that maintain their substance use and work to change those thoughts to more realistic thoughts. Cognitive restructuring can be used in patients with pain and substance abuse to address both of these challenges.

113.2.9 Problem Solving and Goal Setting

CBT protocols for pain management typically include structured problem-solving skills to help patients learn to manage their pain (Somers et al. 2012a). Problem solving can help patients with pain to identify current and anticipated challenges and generate possible strategies to manage the challenge (e.g., brainstorming possible strategies to increase their use of pleasant activity scheduling during the week). Problem solving within a CBT context also includes helping patients to reflect on how well their selected solution worked and what they might change or repeat in the future. Goal setting involves having patients set short- and long-term goals in learning to manage their pain. Patients are often encouraged to break their goals into small steps and set very objective measures of progress (e.g., use the activity-rest cycle for all household activities – use activity-rest cycle while cooking dinner and assess pain levels during activity).

Problem solving and goal setting are both key skills in CBT protocols for substance use disorders, as patients with substance use problems often struggle with delaying long-term pleasure (e.g., sense of mastery that accompanies abstinence) for short-term pleasure (e.g., euphoria of drug use) (McHugh et al. 2010). Thus, these strategies could be used to simultaneously address challenges related to both pain and substance abuse.

113.2.9.1 Cognitive-Behavioral Strategies Applied to Patients with Chronic Pain: A Selected Review of Empirical Work

CBT has been widely studied as an intervention strategy for patients having chronic pain. Below we highlight results from studies using several pain populations and highlight the variability of the application of CBT.

An early study published in 1990 by Keefe et al. (1990) examined the effects of a CBT intervention designed to reduce pain, physical disability, psychological disability, and maladaptive pain behavior in patients with osteoarthritic knee pain. This CBT intervention was compared to arthritis education and standard care. The CBT protocol in this study was delivered during 10 weekly, 90 min, group sessions and taught patients the skills of relaxation, imagery, distraction, activity-rest cycling, pleasant activity planning, and cognitive restructuring. Study results showed that patients who received the CBT protocol had significantly lower levels of pain and psychological disability following treatment than patients in the other two conditions. Since this time, much work has been done applying CBT protocols to improve patients' level of pain. Subsequent research has included testing CBT protocols in patients with other types of pain conditions, involving family members in CBT pain management protocols, and increasing the reach and accessibility of such interventions (Somers et al. 2012a; van Hooff et al. 2012; Carmody et al. 2012; Radojevic et al. 1992). Below we present some studies that highlight these advances.

In a study done in the Netherlands (van Hooff et al. 2010), the investigators examined the impact of a residential, 10-day CBT program for patients with chronic low back pain. This program involved 100 h of participant contact time delivered in

a 2-week group-oriented, residential setting. The program components included a stretch and exercise program, education to explain chronic pain, and the use of CBT skills including activity planning, activity pacing, cognitive restructuring, and several relaxation techniques. In the year following the program, participants improved on measures of daily functioning and overall quality of life. A follow-up study (van Hooff et al. 2012) found that 2 years after the program, patients maintained these results and reported decreased use of pain medication and health-care services. This CBT program may be a particularly good model to consider in patients with pain and substance use problems. The inpatient nature of the pain management program may provide an intervention delivery modality that could combine CBT interventions for pain management with common inpatient interventions for substance abuse problems.

While in-person CBT interventions have long been the norm for treatment delivery, an increasing amount of work is being done examining the use of telephone and mobile health technologies (mHealth) to deliver CBT pain management interventions. Interventions delivered by telephone or mHealth technologies are enticing because the delivery reach is greater (e.g., patients can access these from their home if they are not close to a center that provides the intervention) and patient burden is reduced (e.g., travel time, rearranging schedule, physical burden of in-person sessions). Carmody et al. (2012) examined the effectiveness of a telephone-based CBT program in managing chronic in older military veterans. This study was a randomized controlled trial and compared the CBT intervention to a pain education intervention. Interestingly, results of this work found that both CBT and pain education led to improved physical and mental health and reduced pain and depressive symptoms. Pain catastrophizing mediated improvements in these outcomes (i.e., physical and mental health, pain and depressive symptoms). This study demonstrates that a telephone-based intervention can lead to improvements for patients with chronic pain.

In a recent study, published by our group (Somers et al. 2012a), we examined the utility of pairing two psychosocial interventions to benefit patients who suffered from chronic pain and obesity. In our work, we used a randomized controlled trial to examine the long-term efficacy of a combined pain coping skill training (PCST) and lifestyle behavioral weight management intervention (BWM) in overweight and obese OA patients. We found that patients who received the combined psychosocial intervention of PCST+BWM demonstrated significantly better outcomes on key variables including pain and weight compared to patients who received either treatment alone or standard care. This study should serve as model for providers who treat patients who have both chronic pain and substance abuse. When a patient experiences dual challenges, it may be necessary to address both challenges to provide patients with the optimal benefit.

In addition to CBT pain management strategies that teach skills to the patient with chronic pain, there is work that supports involving both the patient and the patient's partner in the treatment of chronic pain. Including partners in interventions for chronic pain expands the application of the biopsychosocial model of pain in psychosocial interventions, as the basis of the model is that pain is influenced by

biological, psychological, and social factors in a cyclic manner. There is evidence that suggests that when patients with chronic pain are adjusting well to their pain, their partner's biological, psychological, and social adjustment is also improved. Likewise, there is evidence that suggests that a partner's adjustment to the patient's chronic pain also impacts the patient in each of these domains. From a clinical perspective, providers often comment that the dynamics of a patient-partner relationship can have a significant impact on how the patient is adjusting to and managing chronic pain.

Intervention studies have examined the value of including partners in psychosocial interventions for treating chronic pain. One of the first studies to do this was by Radojevic et al. (1992) and examined the use of family support in teaching patients with rheumatoid arthritis to manage their pain. This study found that behavioral therapy with a family component led to improvements in joint swelling and pain compared to intervention without a family component and standard care. Other work by Keefe et al. (1996, 1999) has found that when patients with osteoarthritis pain are randomized to a pain coping skill training protocol with or without spouses, patients in the spouse intervention had the best outcomes posttreatment. Interestingly, patients in the spouse intervention showed the longest maintenance of treatment gains showing improvement up to a year following treatment.

This concept of including family members and partners in psychosocial interventions for patients with chronic pain and substance abuse problems may be particularly important and beneficial. Substance abuse programs and intervention protocols very often include partners, other family members, and even friends and other acquaintances (McHugh et al. 2010; Hunt and Azrin 1973; Epstein and McCrady 1998). In fact, there are several theoretically based substance abuse treatments with empirical support that suggest that including patients' significant others in treatment is a critical component to treatment (McCarthy 1999). Studies have found that substance abuse interventions that include a patient's partner or family are more effective than interventions that do not include others in improving substance use outcomes (Fals-Stewart and Birchler 2001; McCrady et al. 2009). While there is limited research examining the combined value of psychosocial interventions for individuals with chronic pain and substance abuse problems, work in each of these fields suggests that such treatments may result in a synergistic impact for patients struggling with these issues.

113.2.9.2 Acceptance-Based Psychosocial Approaches to Pain Management

There has been growing interest in the use of acceptance-based therapies for pain management. Acceptance and commitment therapy and mindfulness-based therapies are commonly used for patients with chronic pain and have been studied in clinical trials. Acceptance and commitment therapy (ACT) is an empirically based psychological intervention, derived from cognitive-behavioral therapy (CBT), which focuses on acceptance and mindfulness processes and commitment and behavioral change processes. ACT targets ineffective control strategies and helps

individuals learn to accept what they cannot control in life and commit to actions that are grounded in their values (Hayes 1999).

The primary therapeutic process in ACT is psychological flexibility, including processes such as acceptance, awareness, present-focused interactions, living by one's value system, and an ability to balance acceptance and change behavior (Hayes 1999). By cultivating psychological flexibility, chronic pain patients may be able to change their relationship with painful thoughts and feelings by accepting their present experience (e.g., pain sensations) and engaging in behavior grounded in their values (e.g., engage in activities that improve their day-to-day discomfort – activity pacing).

A recent review and meta-analysis concluded that acceptance-based treatments (i.e., ACT, mindfulness) have small to moderate effects on pain, depression, anxiety, physical well-being, and quality of life for patients with chronic pain (Veehof et al. 2011). Among the randomized controlled studies that assessed the efficacy of ACT interventions for chronic pain patients, results indicated that there were significant improvements in both physical (i.e., pain disability, sick days) and psychological (e.g., depression, life satisfaction) outcomes (Bruckstein 1999; Dahl et al. 2004; Wicksell et al. 2008).

To date, there has been no published research investigating the efficacy of ACT for chronic pain patients with substance abuse problems. However, ACT-based interventions have been utilized in substance abuse populations, and preliminary evidence suggests that ACT could be beneficial for individuals with substance use problems. Specifically, ACT has demonstrated positive outcomes for opiate addiction, chronic marijuana use, alcohol abuse, and nicotine dependence (Hayes et al. 2004; Twohig et al. 2007; Petersen and Zettle 2009; Gifford et al. 2004). A recent randomized clinical trial demonstrated that a group-based week-long ACT intervention led to long-term reductions in shame, fewer days of substance use, and higher treatment attendance among patients with substance use disorders (Luoma et al. 2012). The results of these studies suggest that ACT-based interventions might help individuals with substance use problems relate to difficult thoughts and emotions (e.g., shame) with acceptance and mindfulness, instead of by avoiding challenging internal experiences and engaging in conditioned responses like substance use. It appears that ACT has the potential to benefit chronic pain patients with substance abuse problems by helping them accept difficult thoughts and feelings (e.g., distress, pain), potentially reduce their substance use (e.g., pain medication-seeking behavior), and increase their commitment to values-based pain management behaviors (e.g., activity pacing).

Mindfulness-based stress reduction (MBSR) is another acceptance-based intervention for chronic pain. MBSR is a group-based intervention that originated from Eastern spiritual practices and focuses on utilizing meditation to cultivate awareness of one's moment-to-moment experience in a nonjudgmental and accepting manner (Kabat-Zinn 1990). Through the practice of mindfulness meditation techniques (i.e., body scan, sitting meditation, hatha yoga) and group dialogue related to meditation practice and stress management, individuals learn how to accept the present moment, not react in a conditioned way, and utilize effective coping skills

when facing physical states, emotions, or thoughts, such as those related to chronic pain.

Systematic reviews have demonstrated the feasibility and efficacy of MBSR and mindfulness-based interventions on psychological and physical outcomes among healthy and clinical populations (e.g., lower anxiety, improved immune markers) (Bohlmeijer et al. 2010; Matousek et al. 2010; Chiesa and Serretti 2009). Interestingly, there has been growing evidence for the use of MBSR interventions among patients with chronic pain. A recent review indicated that mindfulness-based interventions can lead to nonspecific effects related to the expectation of pain reduction and an improvement of depressive symptoms among patients with chronic pain (Chiesa and Serretti 2011). Additionally, mindfulness-based interventions have been shown to lead to greater pain acceptance and tolerance, compared to control conditions. This research suggests MBSR and mindfulness-based interventions can help chronic pain patients relate differently to their thoughts and feelings (e.g., increased awareness and acceptance of distress and pain).

Preliminary research has also indicated that MBSR and mindfulness-based interventions can lead to improvements in substance use-related outcomes (e.g., decreased substance use and psychological distress) (Zgierska et al. 2009). Conceptually, MBSR would be posited to increase an individual's awareness of their thoughts and feelings (e.g., distress, cravings) and help them mindfully respond to such sensations, instead of automatically reacting and engaging in substance use behaviors. In light of this research, it is possible that mindfulness-based interventions could offer psychological and physical relief to chronic pain patients suffering from substance use problems.

113.2.10 Substance Abuse Treatment Strategies to Use Within the Context of Psychological Pain Management

Psychological approaches, particularly CBT-based protocols, to pain management have been shown to be efficacious. Psychological approaches largely target patients' behaviors (e.g., activity avoidance), cognitions (e.g., pain catastrophizing), and affect (e.g., depression). Behavioral techniques are also commonly used within the context of pharmacotherapy for patients with pain who are prescribed certain medications (e.g., opioid) and/or have a history of substance abuse problems. Behavioral techniques include strategies such as an opioid agreement contract, frequent brief visits to monitor adherence, prescription of a limited number of pills at a time, and toxicology screens. There are also several self-report questionnaires and interviews that are used to assess patients' risk for opioid abuse and their adherence (vs. nonadherence) to pain medication. These behavioral techniques and self-report assessments could effectively be integrated or used conjunctively with psychological approaches to pain management. Perhaps most important in monitoring and attending to substance abuse problems in patients with chronic pain is capitalizing on collaborative treatment planning between all providers and the patient.

113.2.10.1 Opioid or Other Medication Agreement or Contract

Medication agreements or contracts are a common approach to reducing the risk of substance abuse problems in patients with chronic pain who are at risk for substance abuse (Manchikanti et al. 2008). These contracts include objective and specific details of medication treatment, lay out the responsibility of the patient and the provider, and outline the consequences the patient will face if they do not meet their responsibilities (Fishman et al. 1999). Medication agreements or contracts may also include educational information about medications, emergency issues, and legal considerations. This type of document and exercise could easily be integrated into the psychosocial treatment protocols described above. For instance, part of the educational information could include a list of pain coping skill strategies (e.g., relaxation, pleasant activity) that the patient could engage in instead of misusing a substance. There is evidence that medication agreements or contracts reduce abuse of pain medications (Fishman et al. 1999; Fagan et al. 2008). Medical providers have reported that initiating a medication contract with patients is a useful tool for discussing potential problems related to medication misuse. They also have reported that medication contracts decreased many of the problematic behaviors often noted in these patients (e.g., reducing patients' use of multiple providers, decreasing request for early refills, identification of patients likely misusing pain medications) (Fagan et al. 2008).

113.2.10.2 Frequent Brief Visits to Monitor Adherence and Limited Prescriptions

Another strategy that some providers have reported to be helpful in decreasing substance abuse and misuse in patients with chronic pain is frequent monitoring of adherence by having patients see a provider often. Psychosocial intervention protocols provide a good platform to increase patient contact with providers. Psychosocial pain interventions are often delivered in weekly sessions. Patients who are attending weekly sessions to learn new strategies for pain management have frequent contact with a provider. In this way, monitoring patients' adherence may be integrated into the psychosocial intervention, or patients may visit their medical provider at the beginning or end of the psychosocial protocol to monitor adherence.

This close and scheduled contact with providers in the context of a psychosocial intervention protocol may improve adherence in several ways. First, it may increase the patients' sense of accountability and thus decrease their likelihood in engaging in problematic substance abuse behaviors. Second, problematic behaviors are more likely to be identified early by providers, and problem solving can be implemented before the substance misuse becomes chronic and/or out of control. Third, the patient will learn strategies to manage their pain in the context of the psychosocial intervention, and new treatment strategies can be implemented for patients whose pain is not being adequately managed. Many health-care providers who prescribe pain medications find it helpful to give patients a limited prescription amount, forcing patients to stay engaged in regular contact with the provider to receive additional medications.

113.2.10.3 Toxicology Screenings

There is evidence that using toxicological screenings to gather objective information about medication intake and other substance use can reduce substance misuse (Riddle et al. 2012). Patients with chronic pain who are using opioid medications may be tested at the start of treatment and at regular intervals during treatment to determine the presence of opioids and/or the presence of other substances related to problematic behavior (Hammett-Stabler et al. 2002). Urine testing for the presence of absence of substances is common, is fairly non-burdensome for patients, is reliable, and has a low cost (Manchikanti et al. 2008). Toxicology screenings are a strategy that could easily be incorporated into psychosocial pain management intervention protocols for patients who are at risk for substance abuse problems. We suggest that if this monitoring strategy is deemed important for particular patients that patients agree at the initiation of the psychosocial intervention to provide a urine sample at each session. It is important that the patient understand the purpose of the screen, what substances are being considered, and the outcome if substance levels indicate negative substance use behaviors. For instance, it is necessary to alert the providers who prescribe the patients their medications of any problems and that the patient understands that their provider will have access to the information yielded from the screen. Careful communication is critical in psychosocial interventions for patients with pain and substance abuse; missteps in communication by providers or misunderstanding by patients have the potential to undermine intervention benefits.

113.2.10.4 Monitoring with Questionnaires or Interviews

There are several self-report questionnaires and interviews that have been developed that assist in identifying patients' medication abuse (or problematic behavior) and adherence to pain medication over the course of treatment. These assessment techniques are often standard practice for patients who are receiving opioid medications for chronic pain and could be used within the context of psychosocial pain management intervention protocols. These assessments may be used at the initiation of a psychosocial pain management intervention to gather important information about a patient and tailor the intervention to their needs. Assessments may also be used at regular intervals during the course of the intervention to monitor for problematic substance use behaviors and to document improvements that patients participating in psychosocial interventions may be making.

One reliable and valid assessment instrument that may be helpful in this context is the Addiction Behaviors Checklist (ABC) (Wu et al. 2006). The ABC is a 20-item instrument that was designed to help providers monitor ongoing and current behaviors characteristic of prescription opioid medication addiction in patients with chronic pain. The ABC consists of a checklist of observable behaviors that are noted during an interaction with a provider and heard about between clinic visits. A provider completes this checklist. Within a psychosocial intervention, the provider (e.g., psychologist, social worker) who provides the intervention could be trained to complete this instrument and keep track at regular intervals of the patients' medication use. Another valid and reliable assessment tool is the Pain

Assessment and Documentation Tool (PADT), (Passik et al. 2004) which is an interview-based measure that can be included in the patient's medical record. This simple charting device takes approximately 5 min to complete and focuses on four key areas: analgesia, activities of daily living, adverse events, and potential aberrant drug-related behaviors (e.g., requests frequent early refills, changes in route of administration). Within a psychosocial intervention, this tool could be completed by the provider delivering the psychosocial intervention and shared with the prescribing provider if any problems are noted. Other assessment tools such as the Prescription Drug Use Questionnaire (PDUQ) (Compton et al. 1998) are also available. Providers are always encouraged to consider the needs of their patient population and determine a good fit with a validated and reliable assessment tool.

A challenge of formal assessment tools in any context is incorporating them into busy clinic settings with limited staff resources. While incorporating them into psychosocial pain management interventions may eliminate some of this challenge, repeated and consistent formal assessment can still be difficult. All providers (e.g., prescribing physicians, psychosocial interventionist, support staff) working with patients with chronic pain should be taught to be aware and monitor key high-risk behaviors that can reflect substance abuse problems (Manchikanti et al. 2008). Chabal and colleagues (1997) recommend consistently assessing and documenting the following high-risk behaviors: (a) an overwhelming and persisting focus on drug-related issues during pain clinic visits; (b) a pattern of early refills or problems associated with their prescription; (c) multiple telephone calls or visits with requests for more medication; (d) reports of lost, spilled, or stolen medications; (e) obtaining opioids from multiple providers, emergency rooms, or illegal sources; and (f) escalating medication use in the absence of an acute change in the medical condition.

113.2.10.5 Collaborative Treatment Planning

There is evidence that to successfully manage chronic pain, particularly in the context of substance abuse problems, a collaborative treatment planning model between health-care provider and patient is critical. While psychosocial pain intervention protocols can provide patients with many benefits, it is necessary that the psychosocial interventionist works closely and collaboratively with the medical providers and patient to provide the best care. Within this model, the patient is encouraged to participate in treatment planning – their knowledge about their pain, support network, resources, daily life, and values and beliefs are capitalized on in designing a treatment plan. This model also allows the psychosocial interventionist to introduce pain management skills being learned by the patient to the prescribing provider. In this way, the prescribing provider can use language similar to that used by the psychosocial interventionist and encourage the patient to engage in pain management skills they have found particularly helpful. Collaborative treatment planning includes providing patients with the potential benefits and risk of certain pain medications and agreement upon treatment goals between all parties involved. Involving patients in treatment planning may increase the patients' investment or commitment to a treatment (Rains et al. 2006). Increased

investment and commitment is likely to improve patients' adherence to pain medication adherence, increase their use of adaptive pain management skills, and ultimately lead to decreased pain and distress (Rains et al. 2006).

113.2.11 Recommendations and Future Directions

Patients with chronic pain often face a challenging course that is complicated when they have problems with substance use or abuse. Using a biopsychosocial approach to treat patients with these common, comorbid problems may provide the greatest benefit to patients. As mentioned above, the biopsychosocial model suggests that pain management is best approached by simultaneously addressing pain through biological (e.g., rehabilitation, pharmacotherapy), psychological (e.g., behaviors, cognitions, affect), and social (e.g., relationships, recreation) mechanisms. Throughout this chapter, we have presented information on how behavioral and cognitive strategies, with a focus on CBT, are used or could be used to address patients with pain who have substance abuse problems. There is surprisingly limited literature, to date, on psychosocial interventions designed to address both chronic pain and substance abuse problems. There is evidence that CBT for substance use problems is efficacious, (McHugh et al. 2010), yet despite the high prevalence of substance abuse problems in patients with chronic pain, little work has been done examining a psychosocial intervention designed to address both of these challenges.

There have been numerous investigations conducted to examine strategies for using psychosocial strategies to help patients manage chronic pain as well as substance use problems. Separately, these interventions have been shown to be efficacious for the target problem. Perhaps the most obvious area for future work is to examine how CBT and other psychosocial strategies that have been applied to either chronic pain or substance abuse might be combined into an intervention to address both chronic pain and substance use problems.

The sampling of CBT programs for pain management presented above provides a number of treatment delivery modalities that might be used and/or combined to provide a CBT-based intervention that can address comorbid pain and substance abuse problems. CBT pain management programs have been successfully delivered in brief interventions and intensive interventions, as well as been applied to the patient alone or to the patient and a significant other in their life. Past work has also shown that two challenging areas (e.g., pain and obesity) can be intervened on with one synergistic CBT program.

There are several possible combinations of intervention modalities that may be successfully applied to this patient population. Some patients may benefit from the application of simultaneous intervention for both chronic pain and substance abuse problems. Others, however, may need to learn CBT and other psychosocial strategies for either pain or substance use problems first, followed by a subsequent intervention for the secondary challenge. There is also the option to combine treatment modalities such that one component of an intervention (i.e., substance

use treatment) may be delivered in person, while another component of the intervention (i.e., CBT for pain management) is delivered by telephone or an mHealth modality. One challenge of psychosocial interventions has been the maintenance of treatment effects without booster or maintenance sessions. Combining delivery modalities such that the core part of the intervention is delivered in person and the booster is delivered through mHealth technologies may provide the most benefit to patients with chronic pain and substance use problems.

Patients with chronic pain and substance abuse problems may face difficulties in accessing psychosocial intervention programs that can help them manage these challenges. Difficulties accessing interventions may be due to practical barriers such as distance from the medical center, time away from work or family, cost and availability of transportation, or physical/emotional barriers such as the difficulty of travel, the hassle of parking/walking to an appointment, and physical challenges such as pain or other problems. Health-care providers who treat patients with these comorbid challenges should consider these challenges and focus on helping patients to access psychosocial interventions for pain and substance use problems. Mobile health (mHealth) technologies are increasingly being used to manage patients' medical care at all levels and may provide the infrastructure necessary to provide support for patients suffering from chronic pain and substance abuse problems.

Given the prevalence of comorbid chronic pain and substance use problems and the promise provided by a biopsychosocial approach to these challenges, it seems timely that both clinical practice and research would begin to focus on (1) the integration of psychosocial interventions that can address pain and substance use problems and (2) ways to help patients access these interventions. There is an increasing focus on designing intervention trials that are patient centered and adaptive (Schneeweiss et al. 2013). This type of intervention trial applied to psychosocial interventions may be well suited to begin to answer questions such as (1) should both chronic pain and substance abuse problems be intervened on simultaneously or should one be addressed first and another subsequently, (2) what duration of intervention is most effective (i.e., is ten weekly sessions more beneficial than two intensive weeks?), (3) what format is most effective and/or what format do patients prefer (i.e., group, individual, or a combination), and (4) what delivery modality is most effective while also being highly accessible to patients (e.g., is face-to-face, phone, mHealth, or a combination best?).

113.2.12 International Perspectives

There is a strong evidence base for chronic pain programs that are interdisciplinary and adhere to a biopsychosocial model of intervention (Turk 2002; Hoffman et al. 2007). Treatment in interdisciplinary programs typically includes cognitive and behavioral strategies for pain management integrated with medication management and graded physical exercise. In the United States, there has been a rapid decline in pain programs that approach programs from a biopsychosocial model

(Jeffery et al. 2011) (i.e., multidisciplinary pain programs), while there is some evidence that such programs are increasing in other countries. Detailed reasoning for the rapid decline in this promising treatment modality is beyond the scope of this chapter, but it is largely agreed that the main reason for the dramatic drop is due to the US health-care system and insurance reimbursement. Schatman (2012) presents data from a number of countries, including the United States, and details that multidisciplinary pain programs in countries besides the United States are increasing their programs. Of the 12 countries surveyed, only the United States demonstrates a decline in such multidisciplinary programs. Given the complexity of treating patients with pain and substance abuse problems, interdisciplinary programs are likely promising for providing benefits.

113.3 Conclusion

Chronic pain is common and difficult to manage, and it is a major public health and health-care problem (Gallagher 1999). There is evidence that using a biopsychosocial model provides the most comprehensive care and improved outcomes to patients with chronic pain. This approach may be critical for patients with chronic pain who have a history of and/or are at risk for substance abuse problems. We have presented information on cognitive-behavioral and other psychosocial approaches to pain management in the context of substance abuse problems. There are a number of promising approaches that would likely benefit patients with chronic pain and substance abuse problems, yet there is limited work detailing these types of interventions. Future work, from both a clinical and research standpoint, should strive to move this area of knowledge forward by systematically studying approaches to treating patients who struggle with the dual challenge of chronic pain and substance use problems.

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Multidisciplinary Management of Acute and Chronic Pain in the Presence of Substance Use Disorder

114

Daniel L. Krashin and Jane Ballantyne

Contents

114.1 Introduction

Substance abuse and addiction have created crises in many countries, rich and poor, in many areas but particularly affecting health care. Addiction has continued to be a highly significant public health issue for decades, while the specific drugs of abuse have changed over time. In rich countries, prescription drug

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addiction has become a particularly challenging issue and area of rapid growth. This development has particularly affected prescription opioids in North America, as they are prescribed there in greater amounts to more patients than anywhere else in the world, particularly for nonmalignant pain conditions. The increase in the number and dosage of opioid prescriptions here has been dramatic and widespread in all aspects of medicine (Boudreau et al. 2009).

The practice of pain treatment has been significantly complicated and degraded by this growing problem in multiple ways, including the significant population of pain patients who have comorbid addiction issues, but also the structural effects that this growing illicit use of prescription opioids has had on pain practices. There are regular reports of pain clinics being shut down by regulatory agencies for illegal or incautious prescribing practices. Some of these are so-called pill mills which primarily exist to provide opioid prescriptions for profit, but others are well-meaning providers who are manipulated or taken advantage of. Some pain patients are known to continue to seek regular refills of their medications despite no longer needing them in order to resell them; this is said to be particularly prevalent in patients on fixed incomes. Other patients who divert may be actual addicts who engage in doctor shopping and seek out physicians willing to prescribe drugs in large amounts and in high doses. Alongside these frankly abusive pseudo-patients, there are a much greater number of pain patients who have developed aberrant use of their opioids or actual opioid addiction after being prescribed opioids chronically for a pain condition. These patients are complex and challenging and are at high risk for bad outcomes in multiple respects – their pain is unlikely to improve, and they are more likely to experience increased morbidity and mortality associated with opioid use. Prescription opioids are now causing more deaths than either heroin or traffic accidents in some states (Maxwell 2011). This rise in mortality appears to parallel the rise in the availability and strength of prescription opioids for noncancer pain.

The interaction between pain treatment and addiction can be complex and hazardous. Treatment of pain with opioids raises iatrogenic addiction risk (Ballantyne and LaForge 2007). In the United States, illicit drug use was estimated by government survey to be almost 9 % (Substance Abuse and Mental Health Services Administration 2011). The prevalence rate of addiction in patients with chronic nonmalignant pain is estimated to be as high as 48 % in some populations (Morasco et al. 2011a). While some subgroups of prescription opioid abusers, such as youth, are clinically similar to other substance abusers (Catalano et al. 2011), there is a wide spectrum of illness, and many of the older pain patients who develop problems with opioids have significant physical and psychiatric comorbidities, particularly females (Cicero et al. 2012). A large population-based study of opioid use in the general US population found that over half the surveyed population was using prescription opioids that are either not prescribed for them or using prescribed opioids in an inappropriate manner (Green et al. 2011).

114.2 Addiction in the Context of Pain

114.2.1 Addiction Complicates the Treatment of Pain

Worldwide, the case of opioids as treatment for cancer pain remains strong, and there are many areas which suffer from a significant lack of access to these powerful analgesics. However, the initial promising picture of opioids for chronic pain has appeared more and more troubled as evidence of the riskiness of this treatment has become apparent (Ahlbeck 2011). In addition to the addiction issues, the risk of mortality also rises as the dose and duration of chronic opioid treatment increases (Paulozzi et al. 2012).

Patients with addiction are more challenging and risky to treat for pain for multiple reasons. For patients who are actively using, there is naturally a high risk that the opioids will simply add into the mix of drugs that are being abused, with potentially lethal results, particularly if the patient is also using sedative/hypnotics or alcohol. Active substance use also decreases adherence to treatments and can make patients less able to attend follow-up appointments or physical therapy appointments reliably. Active substance abuse is also considered a contraindication for some pain-relieving procedures due to increased risks.

For patients with addiction in remission, treatment with opioids may be a trigger for relapse in their drug of choice, and they are also at increased risk of developing addiction problems with their prescribed opioids.

114.2.2 Diagnosis and Assessment of Addiction in the Pain Treatment Setting

The diagnosis of addiction in psychiatry has been complicated by a distinction between substance abuse and substance dependence. This has always been a poor fit for the particulars of opioids, which cause a withdrawal syndrome in everyone who takes them chronically, regardless of addiction issues. This will be resolved in the forthcoming DSM-V which should have only the diagnosis of substance dependence (O'Brien 2011). While all long-term opioid patients will develop withdrawal with sudden discontinuation, not all will develop the ASAM-APS-AAPM criteria for addiction or impaired control over use or compulsive use, continued use despite harm, and preoccupation with use or cravings (Heit 2003). It should be said, however, that some patients on chronic opioid therapy will go on to develop these addiction symptoms, even without past histories of substance problems or other clear risk factors.

Addiction can be challenging to recognize in many settings, but is particularly difficult in pain clinics, where the majority of patients are in some degree of emotional distress, there is high psychiatric comorbidity with depression and anxiety and frequent occupational and interpersonal problems, and many patients are seeking or are already prescribed habit-forming medications. Studies suggest

Table 114.1 Opioid aberrancies

Escalation of medication dosage
Requesting early refills
Doctor shopping
Losing prescription medications
Tampering with prescriptions

that clinicians may overestimate their ability to recognize substance abusers "by feel" and that they are prone to fall into prejudicial misapprehension, overestimating the prevalence of substance abuse in minority patients and failing to detect it in other population groups.

However, clinicians can reliably observe two important sets of clues to addiction: risk factors and aberrancies. Aberrancies cover a wide spectrum of undesirable, unsafe, or boundary-transgressing patient behavior (see Table 114.1). The use of prescription monitoring programs and urine drug screenings can also be very helpful in identifying aberrant behavior. Once identified, whether by a physician, support staff, or lab, it is important to consider the anomalies in the context of the clinical picture. The differential for addiction includes major mental disorders, delirium, misunderstanding, and interference by family members, roommates, or romantic partners.

Risk factors can be obtained from the patient, his or her other providers, and family. Several standardized questionnaires, such as the SOAPP and ORT, allow providers to identify known risk factors for addiction by self-report at time of intake.

It is important not only to make an accurate pain diagnosis and detect substance abuse in patients but also identify any other psychiatric comorbidities they may have. Once a patient has been identified as having a complex pain problem with addiction or dual diagnosis issues, they need to be evaluated more thoroughly to develop a good understanding of their psychosocial situation, their social and other resources, and significantly their limitations and challenges, including limited resources, legal issues, and family problems (Clark and Treisman 2011).

114.2.3 Acute Pain in Addicted Patients

The evidence suggests that nonaddicted patients in acute pain who have not had opioids before are at low risk for developing addiction during a short course of treatment with low-potency opioids (Skurtveit et al. 2011). However, brain changes of unclear significance are observable after as little as a month of treatment with opioids (Younger et al. 2011). Clinical observations suggest that it is quite difficult for patients to discontinue opioids after 90 days of continuous treatment, which is also the threshold for pain conditions to be considered chronic. It is not unusual in academic pain centers to encounter patients who have undergone procedures and been prescribed pain medication for one, two, or even 3 months before they are referred to the pain service for a subacute problem

which is rapidly becoming a chronic condition. Particularly when a hospitalized patient is nearing discharge, this can be problematic if they continue to require high doses of opioids for pain management but would not be safe to be given prescriptions for large amounts of these.

This situation requires close monitoring to determine what is happening, as the same clinical picture may represent reactivation of addiction and medication overuse, an inadequately treated pain condition, or diversion. Ideally, in the case of elective procedures, these issues can be identified beforehand and incorporated into treatment planning; however, a significant proportion of acute pain patients, particularly those with substance abuse issues, will present with pain secondary to trauma occurring due to assault, injury, or motor vehicle collision with no advance warning. When these issues are identified, they should be incorporated into treatment planning for their care of that acute pain episode and beyond. This can also be an excellent time for substance abuse interventions, particularly if the patient's injury was related in some way to their addiction, as this provides a clear adverse consequence to use as a platform for motivational interviewing or other interventional techniques. Motivational interviewing has been beneficial for preventing alcohol-related reinjury (Gentilello et al. 1999) and for increasing exercise in fibromyalgia patients (Ang et al. 2007), but there is no evidence for MI-based interventions for opioid dependence at this time. At the same time, further psychiatric assessment may be indicated, particularly if there is concern for suicidality prior to hospitalization or during the hospital stay. Some hospitals will have a 12-step-based program meeting on their grounds, and this may also be an option for interested patients to attend if they are healthy and mobile enough.

For pain providers, one challenge of treating the addicted patient for acute pain consists of finding safe and adequate treatments in a population who may have elevated tolerance and decreased ability to manage stress and handle discomfort. In fact, substance abusers have been found to have increased pain perceptions in the emergency department (Neighbor et al. 2011). Perioperative management must take into account patients' use of prescribed opioids, illicit opioids such as heroin, and potentially patients on chronic buprenorphine or methadone for opioid dependence who will have high tolerance and, in the case of the buprenorphine patient, some initial difficulty in getting adequate analgesia due to the partial antagonism of the buprenorphine (Mitra and Sinatra 2004). The provider must also be watchful for signs of other substance toxicity or withdrawal, such as stimulant-inducted psychosis or benzodiazepine withdrawal.

For the pain relief provider, it is important to determine, or at least estimate, their baseline opioid dosage, and then maintain them on a regimen of opioids close to this in potency, with additional opioids available as needed for the acute pain. This may require conversion to parenteral opioids, and frequently, the use of IV PCA analgesia is the safest and most effective strategy for managing their acute pain needs. In cases of thoracic or abdominal surgery or trauma, neuraxial anesthesia using epidural catheters to deliver local anesthetics or opioids can be very effective. Epidural morphine, for example, is ten times more potent than systemic morphine.

Where the pain has a focal source, particularly in an extremity, regional anesthesia, such as using nerve catheters, can block much of the nociception from the injury and thus reduce the need for opioids overall, as well as improve perfusion and recovery time. When patients with extremely high opioid tolerance require systemic opioids, a switch to methadone can often allow a decrease of overall dose. Very high doses of opioids raise the risk of respiratory depression and opioid-induced hyperalgesia, a condition characterized by whole-body pain that only worsens with increased opioid dosing.

114.2.4 Treating Chronic Pain in Addiction

Chronic pain is a highly significant and growing problem as the world's population gets older and more people are surviving significant illness or injury. Addicts are more likely to have all kinds of comorbidities, psychiatric and physical, and have a higher rate of physical injury and chronic pain as well (Karasz et al. 2004). The phenomenon of so-called self-medication for chronic pain is another mechanism by which patients may be exposed to these medications and develop addiction (Rosenblum et al. 2003). Chronic pain has been defined variously as pain lasting more than three or more than 6 months; for our purposes, the ASA description of chronic pain as pain lasting longer than "the expected temporal boundary of tissue injury and normal healing and adversely affecting the function or well-being of the individual" is most germane (American Society of Anesthesiologists Task Force on Chronic Pain Management and American Society of Regional Anesthesia and Pain Medicine 2010). Perhaps the most important fact about chronic pain is that it is chronic; in other words, it should be managed without the expectation of complete resolution, a quick return to premorbid function, or a short horizon for treatment. The effectiveness of chronic pain treatments is also less than those for acute pain, with an average effect size of 40–50 %. Any treatments offered for chronic pain should be safe and able to be provided longer term.

The most vexing question in the treatment of chronic pain, particularly chronic pain in addicts, is that of chronic opioid therapy. Patients prescribed opioids for pain are also likely to use opioids nonmedically. This finding has been seen in military veterans and in the general population (Barry et al. 2011; Edlund et al. 2010). A history of substance use disorder makes it less likely that primary care patients will have good relief after 12 months of treatment for musculoskeletal pain including opioids (Morasco et al. 2011b). When one considers that systematic reviews of chronic opioid therapy for noncancer pain have failed to present strong evidence for the effectiveness of this treatment, the balance of risks and benefits seems fairly unfavorable for this treatment approach, despite its popularity in modern medicine (Chan et al. 2011).

"Adverse selection" is the phenomenon of the sickest and highest-risk patients receiving more opioids for longer and often receiving the bulk of opioid prescriptions in any given population. This phenomenon has been demonstrated in multiple settings including private insurance and public, rural and urban (Morasco

et al. 2011a; Sullivan et al. 2010). Similar findings have also been reported among US military veterans and HIV patients (Morasco et al. 2010; Silverberg et al. 2012). Even in the condition of fibromyalgia, in which there is no real indication for opioid therapy, this pattern of increased dosing among patients with more psychiatric illness, substance abuse, and lower function is seen (Fitzcharles et al. 2011).

The APS-AAPM guidelines published in 2009 for the treatment of noncancer chronic pain may be helpful in guiding treatment, although they are not specifically focused on substance abuse patients (Chou et al. 2009). These patients are often more complex, with layered conditions including substance use disorders, one or more primary pain conditions, and frequently psychiatric comorbidities as well. Although these complex pain patients have been shown to respond better to intensive treatment, the health-care system rarely allows them to receive it (Morasco et al. 2011c). Interdisciplinary pain care, which includes treatment by allied professionals and mental health, has become less and less available in the United States, due largely to coverage and access issues.

In this patient population, then, opioids should be prescribed cautiously, in the knowledge that this is intrinsically risky, and not as a first step in pain management. If the patient is enrolled in substance treatment, or about to be referred, opioids may be incompatible with treatment and should be avoided when possible. These patients should first have the benefit of alternative treatment methods to the greatest extent possible, including non-opioid pain medications, nerve medications that are not addictive, behavioral interventions, and physical interventions such as physical therapy, TENS units, and injections where appropriate.

If opioids are felt to be a necessary part of pain treatment, they should be prescribed at the lowest dose possible. Many experts recommend short-acting opioids used on a schedule. If the patient is converted to a longer-acting opioid, it is recommended that they are not also prescribed short-acting opioids on an as-needed basis. This practice of treating "breakthrough pain," while very helpful in cancer pain, often results in patients taking both their scheduled and as-needed medications daily to the maximum extent possible, increasing risks and total opioid dosage (Manchikanti et al. 2011). It is predictable that some patients will overuse or misuse their medications. Many patients, after an initial good response, will quickly develop tolerance to at least part of the analgesic effect of the opioids and will escalate use on their own or request dosage increases. When opioid therapy is discontinued in these patients with comorbid depression and pain, they are likely to relapse on opioid abuse (Heiwe et al. 2011).

One manualized approach that has been developed for veterans with these comorbidities places heavy emphasis on cognitive behavioral therapy (CBT) and acceptance therapy to address many aspects of recovery, including stress management, increased function, and appropriate use of pain medication. This treatment approach is notable for its embrace of the harm reduction approach, enabling it to be used in patients who continue substance abuse (Ilgen et al. 2011).

Patients in underserved groups with severe psychosocial needs, such as the homeless and refugees, have a high risk of untreated or undertreated chronic pain (Hwang et al. 2011).

114.2.5 Palliative Care in Addicted Patients

Palliative care was defined by the WHO as an approach to treatment which improves the quality of life of patients and their families facing the problems associated with life-threatening illness (Sepulveda et al. 2002). In this specialized arena of health care, the mandate to provide comfort may take precedence over concerns about addiction. While it is rare for patients in this clinical context to develop new addiction issues, preexisting psychiatric and addiction issues may be reactivated or worsen under the stresses of serious illness and may go unrecognized by providers. Untreated alcohol dependence, for example, is linked to other substance misuse and worse outcomes in pain patients (Dev et al. 2011). Some cancer patients are provided with pain medications in larger quantities and dosages towards the end of life than any other type of patient. In addition to addiction, misuse or simple incorrect use due to misunderstanding can put patients at risk. These patients, who may be dependent on others for the management and administration of their medications, are also more vulnerable to diversion of medications by people near them. At the same time, many cancer patients do not receive adequate pain treatment due to access to care issues and also due to patient reluctance to use these medications for fear of addiction (Simone et al. 2012).

Following best practices in these patients can help track their medication use and identify aberrancies earlier. Close monitoring of symptoms and more frequent dispensing of opioids can be useful harm reduction approaches. In larger, well-staffed cancer care centers, even daily dispensation of pain medications may be a useful intervention for selected patients. Pill safes and enlisting family members to dispense daily dosages can also improve safety and reduce the risk of misuse/overuse/diversion. In many cases, the medication misuse is also being driven by complex physical and emotional distress, with combined factors of depression, anxiety, worry about the future, impending death, being a burden on family, how family will fare after the patient's death, and non-pain forms of suffering such as dyspnea, fatigue, constipation, or immobility (Kircher et al. 2011).

114.2.6 Pain Treatment in the Setting of Addiction

The initial assessment should include risk assessment. Once risk factors such as past history of addiction have been identified, or current aberrancies suggestive of substance misuse or dependence are seen, the decision must be made how to respond. Treatment should be individualized; however, there are many best practices that should be routinely followed in pain treatment, particularly as these risk factors and aberrancies may not be identified initially. Patients with fewer risk factors and less severe aberrancy may not require specific changes in treatment beyond closer monitoring. For high-risk patients or those whose aberrancy is more concerning, practices including a written, explicit treatment agreement, compliance checklists, and randomized urine drug screens may be helpful in reducing aberrancy in high-risk

pain patients. Early substance abuse intervention, such as SBIRT or motivational interviewing, may also be helpful (Jamison et al. 2010). For patients with severe ongoing addiction issues or serious aberrancies, such as obtaining opioids from multiple prescribers for routine care or diversion, it is often safest to discontinue opioids with a taper or avoid them if they are not taking them already. Some patients in this position will complain that they are being driven to seek illicit drugs. For ethical and professional reasons, it is recommended to continue to offer these patients the full panoply of non-opioid pain treatments to the extent that they are appropriate. In less severe cases, treatment in collaboration with substance abuse treatment providers may be helpful, along with a highly structured treatment plan.

114.2.7 Best Practices for Risk Management

All patients may be potentially at risk for addiction, and current approaches to risk stratification are very limited. For example, there is consensus that there is a large genetic component in predisposition to addiction, with abnormalities of the endogenous opioid system in particular being linked to increased risk of opioid abuse. However, no standard, evidence-based genetic testing protocol has been introduced. While family history may provide some clues to genetic predisposition, addiction is well known to "skip generations" and is often not openly discussed within families so that the patient may not be aware of relevant history.

Therefore, the concept of universal screening in pain medicine, similar to the use of universal precautions for infection control, is becoming more popular (Gourlay et al. 2005). This universal approach may also serve to reduce stigma and improve the detection of addiction in patients who might not fit the stereotypical image that clinicians hold. For example, opioid dependence is often missed in older adults and in Whites, presumably because the index of suspicion is lower in patients who look more like the typical White male physician (Becker et al. 2011; Vijayaraghavan et al. 2011). This screening and risk stratification may also help use scarce community mental health, pain management, and substance abuse treatment resources more effectively, as low-risk patients remain in the primary care setting as long as they are doing well, while riskier patients are able to access more specialized and interdisciplinary care. Patients with serious psychiatric issues, substance dependence, or both should generally be seen in a setting with the availability of mental health consultation. This model tends to apply most to large cities and areas near academic medical centers; however, telemedicine applications may extend the reach of these specialties into rural areas and isolated regions (McGeary et al. 2012).

Several useful screening tools for determining risk factors for patients include the COMM, SOAPP, and ORT. These are all brief, self-administered tests. The COMM has 17 items; the ORT 8 and the SOAPP come in a full 24-item version and briefer versions (Meltzer et al. 2011). The full version of the SOAPP may be the most effective at predicting future aberrancy (Moore et al. 2009). Note that even if a high score does not automatically translate into "do not prescribe opioids," these tests must always be interpreted using clinical judgment. Since they are self-reported screens

and do not attempt to conceal the nature of the assessment, they may underestimate risks in patients who are unreliable historians or deliberately deceitful.

The use of an opioid treatment agreement is also widespread, although there is very little evidence to support its efficacy. The greatest usefulness of this measure is to provide a transparent means of disclosing treatment policy to patients in advance. It is important to discuss the agreement with patients, along with obtaining fully informed consent for any treatments and documenting it. Since the risks of opioid therapy are much better appreciated now than they were even a decade ago, it is not safe to assume that a patient who is seen already on chronic opioids has full understanding of the implications and risks of this treatment. Any specific policies regarding prescription monitoring, pill counts, and urine drug screens should also be discussed at this time.

Urine drug testing (UDT), also known as urine toxicology or "UTox", offers the promise of letting the prescriber know what the patient is exactly taking. In practice, given the multiple metabolites that may be observed even with monotherapy, it is important that an expert reviews these results, whether pain specialist, pharmacist, or lab medicine specialist. UDT is most helpful in demonstrating that patients are not taking prescribed medications or are taking additional, non-prescribed medications or illicit drugs. A policy should be developed to guide providers consistently on what actions to take in the event of an unexpected UDT result. Some studies have shown that even when UDT is obtained and shows unexpected results, prescribers continue to prescribe opioids (Gupta et al. 2011). In some states, where the state law recognizes a role for medical marijuana, providers may choose to obtain UDT without checking routinely for THC. UDT is not able to reliably determine whether a patient is taking the full dose of their prescribed medication. These limitations aside, UDT helps providers recognize aberrancy that would not be identified by behavioral monitoring (Katz et al. 2003). In the United States, many health insurances will not cover the cost of UDT, so providers must make smart choices about when and how often to order them. Systematic reviews suggest that the benefit for patients of standard UDT policies is modest (Starrels et al. 2010).

114.2.8 Cooperation with Allied Providers

Pain providers cannot be expected to master the fields of psychiatry and addiction, but must understand enough to recognize patients with these issues, make appropriate referrals, and collaborate with the appropriate allied providers. It is important to provide solid information to colleagues about the nature of the patient's pain diagnoses and their treatment. For patients with addiction issues, some medications such as benzodiazepines and opioids may be both inadvisable and incompatible with their addiction treatment. In this case, prescribing these medications for the patient may unknowingly sabotage their addiction treatment or provoke relapse.

In patients who have been diagnosed with opioid dependence, a possible option for them may be opioid agonist therapy, namely, methadone or buprenorphine. In the United States, methadone may be prescribed freely for pain, but only

prescribed for the treatment of addiction by federally recognized methadone clinics. In addition, methadone clinics provide patients with a single larger daily dose of methadone, rather than dosing three times a day as is done for pain. Buprenorphine, in the form of Suboxone, may be prescribed for opioid dependence and (off-label) for pain. Buprenorphine is also available without the combination of naloxone, and as a long-acting transdermal patch, Butrans. Both of these forms are more prone to abuse. Since buprenorphine is a partial opioid agonist, it may be less prone to abuse than other opioids, and it is also not suitable for combining with other opioids and may precipitate withdrawal in a patient who has been taking other opioids chronically. Buprenorphine treatment has been shown to be an effective treatment of opioid dependence and also reduces the rush experienced by patients who do relapse and use other opioids on top of the buprenorphine (Jones et al. 2011).

114.3 Conclusion

Substance dependence is a large and growing problem in developed countries. The growth of prescription drug abuse has been particularly concerning. Pain treatment is intimately involved with this explosion in prescription drug abuse, as many of the drugs involved are being ostensibly prescribed for pain and pain patients may be at higher risk for addiction. Many pain patients have comorbid conditions including depression, anxiety, and addiction which complicate their treatment and worsen their prognosis. These patients should be offered the full range of pain management services, with particular emphasis on behavioral interventions; opioids should only be considered, if at all, after reasonable trials of other, safer treatment approaches. Early recognition of the patients by identifying their high-risk status and detecting aberrancies can help with early referrals to mental health and substance abuse providers and cautious, closely monitored prescribing practices.

114.3.1 International Perspectives

The international picture of pain treatment is diverse but can be summed up by region. The Americas have had the greatest increase in opioid consumption over the past 30 years, largely driven by the United States and Canada. Central and South America make some use of oral and injectable morphine for intractable pain.

At the opposite end of the spectrum, Africa has had very little growth in opioid consumption. In general, a small number of developed countries consume most of the world's morphine, and the rest of the world, with most of the world's population, consumes very little (Gilson et al. 2012). These low- and middle-income countries (LMICs) in one study were found to have 83 % of the population but only 9 % of opioid consumption, in part due to fears of addiction and regulatory

barriers (International Narcotics Control Board 2010). For example, a study of opioid prescribing in India followed 1,723 pain patients in Kolkata and did not identify any misuse; most of these patients appear to have been receiving palliative treatment for cancer pain (Karasz et al. 2004; Rosenblum et al. 2003; Gilson et al. 2012; Rajagopal et al. 2001). The Middle East and North Africa are very diverse, but are commonly restrictive in their use of opioid pain relievers except for the wealthy gulf states. Likewise, in the Asian Pacific region, Australia and New Zealand follow the pattern of Western Europe, while other Asian nations use significantly less opioids, and the large, poor, and populous nations of India and China have significant pain undertreatment issues. Japan uses significantly more opioids than other East Asian nations, but much less than Australia and New Zealand, and Japanese physicians have been shown in polls to have very high levels of concern about addiction resulting from opioid treatment of pain (Miyashita et al. 2010).

Africa has the lowest opioid use of any region, and the health providers in sub-Saharan Africa in particular appear to make very little use of opioids even for cancer pain and palliative care (Human Rights 2011).

In many LMICs, opioids are not widely available, even for cancer pain, and there is a significant issue of undertreatment of severe pain (Human Rights 2011). In parts of Eastern Europe and the former Soviet Union, the traditional medical practice was to restrict opioid use to inpatient use for postoperative care, with little or no outpatient opioid use. In the last decade, this has changed, particularly in the treatment of cancer pain; however, acetaminophen and NSAIDs continue to be the mainstay of pain treatment. The EU agency ATOME has promoted a balance between improved pain control and abuse prevention, and much of their efforts have focused on education and legal reform (AtOMiE).

Western European practice tended to avoid chronic opioid therapy in noncancer pain again until the last 10–15 years, when new guidelines came out for responsible opioid use in this population in the early 2000s. At the same time that the use of opioids was being extended in this population, European pain specialists were already noting the same issues that were seen elsewhere: “Chronic pain patients demonstrate a wide range of biological, psychological and social symptoms and complications, and patients referred to specialised pain units usually belong to the most stigmatized groups. Higher prevalence rates of opioid usage among these patients are therefore not surprising. About 70% of patients in our Pain Centre are treated with opioids already at referral in a mean daily dose of about 70 mgs of morphine. High prevalence rates of opioid users have increasingly been reported from other multidisciplinary pain centres” (Eriksen 2003). These fears, expressed by a Danish expert, appear to have been borne out. A more recent study of 253 patients at a Danish tertiary care center found that 14.4 % were considered addicted by ICD-10 criteria and 19.3 by criteria derived from the publications of Russell Portnoy (the DSM-IV is not used widely in Denmark) (Hojsted et al. 2010). As has been demonstrated previously in so many other populations, the addicted population of pain patients was more likely to drink alcohol, smoke tobacco, use benzodiazepines, and be clinically anxious and depressed.

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Section IX

Psychiatric Comorbidities and Complications of Alcohol and Other Drugs

Kathleen Brady and Giuseppe Carrà

Psychiatric Comorbidities and Complications of Alcohol and Other Drugs: An Introduction

115

Kathleen T. Brady and Giuseppe Carrà

Abstract

The co-occurrence of substance use disorders with other psychiatric disorders has been an area of increasing focus over the past 20 years. This more intensive focus has increased the knowledge base with regard to the prevalence of co-occurring disorders, the neurobiological interface between substance use and other psychiatric disorders, and both pharmacologic and psychotherapeutic treatment options. In addition, a critical focus on workforce training and designing systems of care that can optimally address the treatment needs of individuals with co-occurring disorders is needed. In these efforts, sharing knowledge across cultural and national boundaries is essential.

An international perspective on co-occurring disorders is particularly important for a number of reasons. Just as there are cultural influences in definitions, recognition, diagnosis, and treatment approaches to substance use disorders, there are important cultural influences in other psychiatric disorders and in the approaches to comorbidity. As Drs. Ruiz and Salloum point out in their overview, while different countries experience varying levels of recognition of the importance of co-occurrence of substance use and substance use disorders in the mental health-care systems, the concept of "dual diagnosis" is becoming increasingly well accepted, and recognition of the importance of co-occurring disorders is rapidly expanding around the globe. In this context, they emphasize the importance of

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recognizing that "ethnic, racial and cultural groups manifest their medical illnesses, including psychiatric illnesses, within the context of their culture, tradition, beliefs and heritage." The chapters that follow are written by clinicians and scientists from a wide range of countries in an attempt to give the reader a broad and international perspective on the topic of co-occurring disorders.

The chapter on psychotic disorders by Dr. Carretta and colleagues provides an excellent overview of the epidemiology of co-occurring psychotic disorders and substance use disorders as well as a scholarly discussion of potential etiologic connections (▶ Chap. 122, "Psychotic Disorders and Substance Use Disorders"). The area of cannabis and psychotic disorders is particularly well covered as this has been a topic of intense investigation and discussion at an international level for the past 25 years. Drs. Nunes and colleagues have written a comprehensive chapter covering the topic of co-occurring mood and substance use disorders. In particular, their discussion of the approach to differential diagnosis and treatment of individuals with these comorbidities is detailed and useful across global boundaries. Dr. Roncero and colleagues have provided an excellent chapter focused specifically on bipolar disorder and co-occurring addictions. They emphasize the high risk for comorbidity between these disorders and discuss possible reasons for this etiologic interface. Their discussion of subtypes of bipolar disorder often seen with substance use disorders, such as rapid-cycling disorders, is particularly useful for clinicians.

Dr. Bartoli and colleagues have extensively reviewed epidemiological and clinical issues with regard to the comorbidity between anxiety and alcohol or substance use disorders whose etiologic links and temporal relationships are still unclear and, probably, heterogeneous and multifactorial. Alcohol and substances may be misused to self-medicate anxiety, avoidant, and phobic symptoms, but also anxiety disorders may be consequences of alcohol and/or substance misuse. Dr. Levin and colleagues have also provided a scholarly and comprehensive chapter addressing the issue of co-occurring ADHD and substance use disorders. This comorbidity is an issue of particularly concern in the United States where the diagnosis of ADHD has increased dramatically in prevalence over the past 20 years. In this regard, other nations and health-care systems may be able to learn from experiences of the United States concerning potential problems stemming from both under- and overdiagnosis of ADHD. The chapter on substance-induced disorders by Baldacchino and colleagues provides an excellent overview of general concepts in the dual diagnosis and comorbidity literature from an international perspective before an in-depth and comprehensive discussion of specific substance-induced psychiatric syndromes (▶ Chap. 116, "Substance-Induced Mental Disorders"). A "sidebar" in this chapter by Drs. Bonny-Noach and Mell addresses a specific substance-induced syndrome that has been seen with increasing frequency in young Israeli military veterans and is particularly fascinating (▶ Chap. 121, "A Drug Treatment Program for Young Israeli-Military Veterans").

The chapter by Drs. Szerman and Peris addressing the co-occurrence of personality disorders and addictive disorders is of particular interest with regard to providing international perspectives (▶ Chap. 124, "Personality Disorders and Addiction Disorders"). The authors address substantial criticism of the Diagnostic

and Statistical Manual of Mental Disorders (DSM) system of psychiatric diagnosis which may not provide the best approach to co-occurring disorders, particularly when it comes to personality disorders. In particular, the dimensional approach to psychiatric diagnosis and the overlap between Axis I and Axis II disorders which has been recognized and developed more in the European psychiatric literature is relevant to this chapter. Their more positive review of the DSM-5 trait system for the diagnosis of personality disorders is of interest in helping to understand the rationale for the new approach proposed.

In sum, this section provides a thorough and comprehensive review of the co-occurrence of psychiatric and substance use disorders from multiple perspectives. We have much to learn from sharing evidence and observations across cultural and national boundaries in order to develop the most sophisticated understanding of this complex patient population. This improved understanding is essential to expanding treatment options and improving treatment outcomes worldwide.

Substance-Induced Mental Disorders 116

Alex Baldacchino, V. Arvapalli, Anthony Oshun, and Serenella Tolomeo

Contents

Abstract

Comorbidity is a condition describing the presence of two or more diagnosable conditions happening, either at the same time or having a close temporal relationship, to the same individual. This is usually more focused on the presence of psychological/psychiatric problems and associated polydrug use and misuse. This chapter will try to identify and clarify the nature and relationship of the different avenues of clinical presentations presenting as substance-induced mental disorders.

They include:

- Substance use and withdrawal from substances may lead to psychiatric syndromes or symptoms.
- Intoxication and dependence may produce psychological symptoms.
- Substance use exacerbating or altering the course of preexisting mental disorder.

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- A primary mental disorder precipitated by a substance use disorder, which may lead to psychiatric syndromes.

  Although there are several different classification schemes for psychoactive drugs (pharmacological, legal, medical), the most common organization is based on their effect on behavior and cognition. According to this scheme, psychoactive drugs will be classified into three broad categories: (1) sedatives, (2) stimulants, and (3) hallucinogens. Substance-induced mental disorders will be described on the basis of this classification in this chapter.

116.1 Introduction

Four categories of dual diagnosis involving substance misuse have been suggested by Krausz (1996):

- A primary diagnosis of a mental disorder, with a subsequent (dual) diagnosis of substance misuse that adversely affects mental health
- A primary diagnosis of drug dependence with psychiatric complications leading to mental disorder
- Concurrent diagnosis of substance misuse and mental disorders
- A dual diagnosis of substance misuse and mood disorder, both resulting from an underlying traumatic experience, for example, posttraumatic stress disorder

Central to these explanations is the distinction between "primary" and "secondary" in terms of cause and effect. However, the distinction has also been made in terms of temporal appearance or age at lifetime onset (Feighner et al. 1972). While such a distinction has face validity in suggesting that the first temporal disorder is independent of subsequent disorders, it does not clarify whether the secondary disorder is independent of the first or how the disorders may be interrelated (Samet et al. 2004). However, it is widely recognized that certain mental disorders have characteristic ages of onset and can thus be distinguished temporally as primary or secondary. For example, attention deficit disorder (ADD) and conduct disorder begin in childhood; alcohol and drug abuse in early to mid-adolescence; and anxiety, mood, and psychotic disorders in late adolescence and adulthood.

However, the operational use of concepts of substance use and misuse relies heavily on etiology, clinical practice, particular cultures, and ideology (Todd et al. 2004) as well as the purpose(s) behind their use. Berridge points out that "definitions of alcoholism and drug addiction are historically constructed, are the products of particular historic sets of circumstances and interrelationships (Berridge and Edwards 1987; Scull 1981). Disease concepts, for example, may have been common in the 1890s and 1950s, but the components of the theoretical basis were very different in those decades" (Berridge 1993).

Many terms have been used over the last century or more to describe or define problems related to the use of alcohol, drugs, and other substances. Some of these terms are, to say the least, very ambiguous and fluid. It is important to appreciate the latter point since these terms are in turn employed in some of the descriptions or definitions of dual diagnosis, comorbidity, etc. The definition of addiction,

dependence, etc., is key to intervention with substance abusers as it classifies abusive drug/drinking behaviors and impacts on the type(s) of treatment that is given.

116.2 Dimensions of Substance-Induced Mental Disorders

The difficulty of making a diagnosis of a substance-induced mental disorder is because of the different points of view from mental health and addiction services that tend to confuse the situation. Furthermore, Abdulrahim (2001) suggests that the nature and relationship of comorbidity is complex and is so for the following reasons:

- Substance use and withdrawal from substances may lead to psychiatric syndromes or symptoms.
- Intoxication and dependence may produce psychological symptoms.
- Substance use may exacerbate or alter the course of preexisting mental disorder.
- A primary mental disorder may precipitate a substance use disorder, which may lead to psychiatric syndromes.

116.2.1 Examples

116.2.1.1 Cannabis-Induced Mental Disorders

An issue which has caused considerable debate in this area is the precise mechanism of the link between cannabis and psychosis. Specifically, cannabis use may alter the onset, course, and clinical expression of the psychotic episode.

There are several theories including:

(A) Cannabis use occurs as a means of self-medicating for the effects of a prodromal or florid psychosis episode/illness (Khantzian 1985).

(B) Latent form of schizophrenia. Cannabis use interacts synergistically with a predisposition to psychosis to result in the emergence of psychotic symptoms earlier. It assumes that cannabis is just one of many confounding factors, including a genetic predisposition, which precipitates psychosis. According to this theory, the psychosis will not necessarily reduce or cease with a withdrawal from cannabis use and will not present with a distinctive psychopathology (Henquet et al. 2004; Miller et al. 2001).

(C) Cannabis worsens or ameliorates an established psychosis (Caspi et al. 2005).

(D) Cannabis use directly causes toxic effect causing specific psychosis. Psychosis would not occur in the absence of cannabis use, and the fact that cannabis is the cause of the psychosis can be inferred from the symptoms or psychopathology of the psychosis (Ghodse 1986).

(E) Coincidental presentation of two prevalent disorders which peak in a young age group. Understanding how clusters of disorders through either concurrent or sequential links may promote a specific type of psychopathology (Cerda et al. 2008).

Another possibility is that cannabis and associated psychosis are not different from psychotic symptoms in the presence of other substances such as amphetamine, cocaine, and alcohol use. For example, Jordaan et al. (2009) concludes that since patients with alcohol-induced psychotic disorder have fewer negative and disorganized symptoms, better insight and judgment, and less functional impairment compared to patients with schizophrenia, this alcohol-induced psychotic disorder is a distinct entity. This resonates with the conclusions that alcoholic hallucinosis was not a variant of schizophrenia but a distinct condition (Glass 1989).

116.2.1.2 MDMA-Induced Neurotoxic Damage and Mental Disorders

That substance use could cause mental disorders or at least can intensify such problems is supported by both psychological and neurobiological data. For example, it is known that the effect mechanism of MDMA significantly concerns the serotonin system (Battaglia and De Souza 1989; Kankaanpaa et al. 1998; Kovar 1998; Piercey et al. 1990) and chronic MDMA use is supposed to have a neurotoxic effect on the serotonin system (McCann et al. 1994). Since the use of MDMA is linked to decreased sensitivity of serotonin receptors, it is a well-supported assumption that this bodily change could have a significant role in the often experienced symptoms of depression of MDMA users. This view seems to be strong, although it has been often stated that emotional instability might precede substance use, and it may have a role in the development of substance use, thus a circular causality might be assumed.

116.2.1.3 Chronic Opioid Use and Neuropsychological/Cognitive Impairment

Given the current emphasis on patients suffering from co-occurring substance use disorders (SUD) and other Axis I or Axis II mental disorders, one may forget that dual diagnosis can also include patients displaying both SUD and cognitive impairment. For example, chronic exposure to opioids has been reported to be associated with a number of neuropsychological impairments both during active use and after a period of abstinence. A wealth of studies have examined the acute, subacute, and chronic effects of opioids on neuropsychological performance using a broad variety of measures sensitive to component aspects of attention, memory, learning, and executive functioning (Fernandez-Serrano et al. 2011; Ersche and Sahakian 2007).

However, for methodological reasons, defining the nature and extent of opioid-related impairments remains elusive. For instance, research on memory functions has resulted in a number of studies showing impairments in word/pattern recognition, learning and recall of words/figures, paired associate learning, and retrieval (Ersche et al. 2006; Fishbein et al. 2007; Ornstein et al. 2000; Prosser et al. 2006). However, other studies failed to replicate these findings of memory deficits in chronic, opioid-dependent individuals (Davis et al. 2002; Mintzer et al. 2005). In addition to memory function, studies on attention also suggest inconsistent findings. Studies have shown either no impairments in attention (Davis et al. 2002; Soyka et al. 2005) or a significant reduction in attention span (Schindler et al. 2004; Soyka et al. 2008) in chronic, opioid-dependent individuals.

Neuropsychological studies of chronic opioid users have identified similarly inconsistent deficits in executive function measures. These have included impairments in cognitive flexibility (Pirastu et al. 2006), strategic planning (Fishbein et al. 2007), decision making (Brand et al. 2008; Verdejo-Garcia and Perez-Garcia 2007), and risk taking (Prosser et al. 2006; Verdejo-Garcia et al. 2007). However, other studies found no clear deficits when comparing the performance of healthy controls, with that of opioid abstinent, polysubstance users, head injury patients, or patients with chronic pain (Rotherham-Fuller et al. 2004; Gruber et al. 2006).

A meta-analysis by Baldacchino et al. (2012b) suggests that chronic opioid exposure is associated with deficits across a range of different neuropsychological domains. However, the only domains where meta-analysis suggests robust impairment were those of verbal working memory, risk taking, and cognitive flexibility (verbal fluency).

116.2.2 Presentations

Although there are several different classification schemes for psychoactive drugs (pharmacological, legal, medical), the most common organization is based on their effect on behavior and cognition. According to this scheme, psychoactive drugs can be classified into three broad categories: (1) sedatives, (2) stimulants, and (3) hallucinogens. Substance-induced mental disorders will be described on the basis of this classification (Table 116.1).

116.2.3 Sedative-Induced Mental Disorders

Sedatives depress or inhibit brain activity and produce drowsiness, sedation, or sleep, relieve anxiety, and lower inhibition. Although the depressant compounds do not share a common neural mechanism of action, most of them either decrease the metabolic activity in the brain or increase the transmission of the principal inhibitory neurotransmitter of the brain, gamma-aminobutyric acid (GABA). Common depressants include barbiturates, benzodiazepines, opioids, and alcohol (Eşel et al. 2003).

There are several mental disorders presenting as a direct consequence to excessive consumption of alcohol. The conditions presented with benzodiazepine and other sedatives tend to have the same quality but not necessarily severity of the psychopathology arising.

116.2.3.1 Alcohol-Induced Amnesia (Blackout)

Loss of memory is related to periods when intoxicated with alcohol. The anterograde memory loss tends to be as a result of lack of recall rather than registration (Jennison and Johnson 1994). Two types have been identified:

(a) "En bloc" – Discrete start and finish points with complete loss of memory for interim events
(b) Fragmentary – Partial amnesia with islands of recollection still intact

Table 116.1 Substance-induced mental disorders

	Sedatives	Stimulants	Hallucinogens
Acute effects	Relaxation, sedation, disinhibition and impaired judgment, slurred speech, ataxia, nystagmus, auditory hallucinations with delusions, labile mood, stupor and coma. Impairment of motor coordination and cognition	Increased alertness, energy, and confidence; reduced hunger and sleep; euphoria, anxiety, and paranoia	Relaxation, sedation, disorientation, euphoria and increased sensory awareness with hallucinations and delusions. Sometimes dysphoria, an overwhelming sense of fear often leading to panic attacks. Synesthesia
Withdrawal effects	Anxiety, agitation, disorientation, hallucinations (tactile, visual, auditory), and insomnia	Fatigue, anxiety and depression ("crash")	Emotional and behavioral disturbance, anxiety, depression, insomnia, and loss of appetite
Chronic effects	Depressive and anxiety symptoms including guilt and hopelessness confusion, ataxia, ophthalmoplegia, nystagmus, anterograde memory loss, and confabulation. Others include deficits in abstract thinking, perceptual motor skills, and visuospatial and verbal learning	Depressive and psychotic symptoms. Cognitive impairments	Cognitive impairment and possible long-term, anxiety, depressive, and psychotic symptoms. Suicidal ideations. Cognitive impairments

116.2.3.2 Alcohol-Induced Psychosis/Hallucinosis

This mental disorder presents with a sudden onset of auditory hallucinations and delusions in the presence of clear "sensorium" in individuals with a history of alcohol abuse. The auditory hallucinations are usually derogatory in nature or portray negative connotations (Jordaan et al. 2009). These symptoms usually improve quickly (usually within a week) although they can become chronic due to ongoing alcohol misuse they tend to persist. Patients with alcohol-induced psychosis can present with later onset of psychosis, lower educational level, more anxiety and depressive symptoms, fewer negative and disorganized symptoms, and less functional impairment compared with patients with schizophrenia (Jordaan et al. 2009).

116.2.3.3 Alcohol Withdrawal Syndrome (AWS)

This arises in alcohol-dependent patients, usually within 24–48 h of stopping alcohol consumption (McKeon et al. 2008). AWS can occur unexpectedly in an alcohol-dependent patient following hospital admission and intentionally in those seeking abstinence. Alcohol withdrawal is common and usually mild but can also lead to withdrawal seizures and delirium tremens, both of which may be fatal (McKeon et al. 2008). The definition of alcohol withdrawal encapsulates the key

clinical findings of AWS including anxiety, agitation, tremor, delirium, disorientation, hallucinations (tactile, visual, auditory), and insomnia.

116.2.3.4 Delirium Tremens

This is characterized by an acute confusional state with fluctuating levels of cognition and consciousness over the day following alcohol withdrawal in a patient with alcohol dependence. It usually occurs 2–4 days after last alcohol consumption unlike simple alcohol withdrawals which occur within a few hours of stopping alcohol. Autonomic symptoms including sweating, nausea, palpitations and tremor, hypertension, and tachycardia are invariably present. It occurs in about 5 % of withdrawal episodes in admitted patients (Mayo-Smith 1997). Important clinical features include visual hallucinations and severe tremors. Other symptoms include fear, paranoid delusions, and psychomotor agitation.

116.2.3.5 Wernicke's Encephalopathy and Korsakoff Psychosis

Chronic alcohol consumption can result in thiamine deficiency via inadequate dietary intake, malabsorption of thiamine from the gastrointestinal tract, and impaired utilization of thiamine in the cells. Thiamine is an essential cofactor for several enzymes involved in brain cell metabolism that are required for the production of precursors for several important cell components as well as for the generation of the energy-supplying molecule ATP. Accordingly, thiamine deficiency can cause a number of processes that are toxic to brain cells (Martin et al. 2003).

Wernicke's encephalopathy is a relatively common and potentially dangerous neuropsychiatric condition caused by thiamine (vitamin B1) deficiency (Boileau et al. 2006). If not treated it can result in a chronic form of the disease known as Korsakoff psychosis. As a result of the close relationship between Wernicke's encephalopathy and Korsakoff psychosis, reference is often made to the Wernicke–Korsakoff syndrome (Thomson et al. 2002).

The symptoms of Wernicke's encephalopathy include mental confusion, oculomotor disturbances, and gait ataxia (an impaired ability to coordinate movements, particularly of the lower extremities). Patients will also manifest deficits in memory function, abstract problem solving, perceptual motor skills, visuospatial, verbal learning, and motor function.

Korsakoff syndrome consists of memory impairments (preserved primary memory, impaired recent memory, and extensive retrograde amnesia) occurring in clear sensorium. Other psychopathology includes poor insight into the memory deficit with resulting confabulation, absence of impairment of consciousness, and absence of global cognitive impairment (Kopelman et al. 2009).

116.2.4 Stimulant-Induced Mental Disorders

Stimulants produce behavioral arousal. As with the sedatives, there are a variety of substances each with a different neural mechanism of action. These drugs act by increasing the activity of three neurotransmitters in the brain: serotonin, dopamine,

and norepinephrine (Taylor et al. 2013). Examples of stimulants are cocaine, caffeine, and nicotine. Other examples of stimulants are amphetamines and amphetamines-like substances such as methamphetamine. Smoking, sniffing, ingesting, inhaling, and injecting are the most common methods in which these drugs are used.

Stimulant-induced mental disorder presents in the acute stage with euphoria and in vulnerable groups severe anxiety, paranoia, and manic type (increased energy, mental alertness, increased sexuality, and extended periods of wakefulness) psychopathology (McKetin et al. 2013; Harris and Batki 2010). This is associated with improved attention and suppressed appetite (Tang et al. 2009). It can also cause perceptual disturbances especially "formication." This is described as a sensation that resembles that of insects crawling (tactile hallucination) on (or under) the skin. It is one specific form of a set of sensations known as paresthesia, which also include the more common prickling, tingling sensation of "pins and needles." As the effects of the drugs subside, the user feels dysphoric, tired, irritable, and mildly depressed, which may lead to subsequent drug use to regain the previous experience (Shoptaw et al. 2009; Sofuoglu and Kosten 2005).

Chronic use of excessive amounts of stimulants can intensify symptoms or precipitate a psychotic episode similar to schizophrenia in vulnerable individuals (Ujike 2002; Yui et al. 1999).

116.2.5 Hallucinogen-Induced Mental Disorders

Hallucinogens and psychedelics do not share a common mechanism of action, but all induce hallucinations. These drugs can be either natural such as mescaline, which is derived from the peyote cactus, or synthetic such as lysergic acid diethylamide (LSD), but they are typically classified pharmacologically according to the affected neurotransmitter system. Cholinergic psychedelics (drugs altering acetylcholine transmission) include physostigmine, scopolamine, and atropine. Drugs that alter norepinephrine transmission include mescaline and ecstasy. Drugs that alter serotonin transmission include LSD and psilocin. Other drugs in this category include the psychedelic anesthetics phencyclidine (PCP) and ketamine (Nichols 2004; Van Jan et al. 2011; Seivewright and Lagundoye 2000).

Cannabinoids, psychoactive substances derived from the hemp plant Cannabis sativa, are often classified as hallucinogens. There are two types of acute effects on mental function – euphoric and calming. Besides dramatic impact on emotional functions, acute cannabis intoxication can induce cognitive impairments, sometimes persisting for weeks or months following abstinence. This usually presents as fragmentation of thought process, major disruption of temporal understanding, distortion of perceptual stimuli, and poor attention and concentration. "Cannabis psychosis" may not be qualitatively any different from other forms of psychosis (Baldacchino et al. 2012a). Some specific psychopathologies stated include confusion, disorientation, amnesia, depersonalization, delusions, hallucinations, paranoid, ideation, psychomotor agitation, labile affect, and hostility (Amar and Potvin 2007).

Chronic exposure to cannabis leads to a cannabis withdrawal syndrome (Budney et al. 2008) characterized by the frequently reported symptoms of emotional and behavioral disturbance which includes depression, anxiety and irritability, nausea, abdominal discomfort, decreased appetite, weight loss, physical discomfort, and insomnia with strange dreams (Budney et al. 2008). A chronic buildup of cannabinoids produces both short-term and long-term cognitive impairments. There is insufficient knowledge to determine the level of risk associated with cannabis use in relation to long-term psychotic symptom (Minozzi et al. 2010).

116.3 Conclusion

Substance-induced mental disorders are important conditions that need to be contextualized within the substance use history but also need to be well managed to prevent further deterioration. Substance-induced mental disorders also need to be understood within the context of the overall lack of defined and strict operational definitions used in the field of comorbidity/dual diagnosis.

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Co-Occurring Mood and Substance Use Disorders

117

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Abstract

Mood disorders, which include the depressive disorders and bipolar disorders, are prevalent in the general population and are among the most common disorders observed to co-occur with substance use disorders. Mood disorders have been associated with worse prognosis among substance-dependent patients. Further, treatment of co-occurring mood disorders has been shown to improve treatment outcome among substance-dependent patients with improvement in both mood and substance use. At the same time, mood symptoms and syndromes among substance-dependent patients frequently remit when the patient enters treatment for substance dependence and reduces substance use or achieves abstinence – no specific mood disorder treatment required. Thus, it is important for clinicians working with substance-abusing patients to be able to recognize mood disorders in the clinical history, distinguish mood disorders that require specific treatment, recommend appropriate treatment options, and monitor clinical course. This chapter reviews the evidence on the diagnosis and treatment of co-occurring substance and mood disorders, with emphasis on depressive disorders.

117.1 Introduction

The co-occurrence of mood and substance use disorders has been a source of considerable controversy, sparked by the complexity of potential relationships between mood syndromes and substance use. For example, in an alcoholic, do depressive symptoms represent side effects of chronic alcohol exposure that will resolve if the patient achieves abstinence? Or do they represent an independent mood disorder that requires specific treatment, either with behavioral therapy, medication, or a combination of the two? In any given patient, either of these explanations may be correct. Effective management of co-occurring mood symptoms in substance-abusing patients requires a nuanced awareness of the differential diagnosis of the mood symptoms. This chapter will attempt to provide a guideline for clinicians to the differential diagnosis and therapeutics of mood syndromes among substance-dependent patients, based on the current evidence.

The co-occurrence of bipolar disorders and substance use disorders is covered in detail in a separate chapter of this text. However, when conducting a diagnostic evaluation and treatment planning for patient with a substance use disorder and mood symptoms, it is very important to consider bipolar disorders in the differential diagnosis, since the treatment implications are quite different. This chapter therefore provides an overview of the diagnosis of bipolar disorders.

117.2 Prevalence and Co-occurrence

117.2.1 DSM-IV and DSM-5

The publication of this textbook coincides with the recent (May 2013) release of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (American Psychiatric Association 2013). However, virtually all the empirical evidence that will be cited in this chapter, bearing on co-occurrence of mood and substance use disorders, derives from investigations that used DSM-IV (American Psychiatric Association 1994) or earlier criteria sets. The criteria for depressive disorders (major depression, persistent depressive disorder (dysthymia)) and bipolar disorders (bipolar I, bipolar II, cyclothymia) have changed little between DSM-IV and DSM-5. Dysthymia, which in DSM-IV described chronic low-grade depression, has been renamed persistent depressive disorder in DSM-5 and now encompasses both chronic low-grade depression and chronic major depression. DSM-5 added a new category of disruptive mood dysregulation disorder (DMDD) to the group of depressive disorders. DMDD is intended to distinguish children with predominantly irritable mood, but without other features of bipolar disorder, from children in the bipolar spectrum. The substance-induced diagnoses (substance-induced depressive disorder, substance-induced bipolar disorder) are similar conceptually in DSM-5 and DSM-IV with some subtle differences reviewed below.

A thorough review of the diagnostic criteria for depressive and bipolar disorders is beyond the scope of this chapter. Readers who are not familiar with these diagnostic criteria should review the DSM-5 (American Psychiatric Association 2013), which provides detailed descriptions.

The substance use disorders were changed in DSM-5, in that substance dependence (DSM-IV) and substance abuse (DSM-IV) have been combined into one category, named substance use disorder (DSM-5). This was done because the weight of the evidence indicated the criteria for DSM-IV substance abuse, which involved hazardous use (e.g., driving while intoxicated), social or interpersonal problems related to use, or failure to perform in major role responsibilities, were intermixed across the severity spectrum with substance dependence criteria, representing part of a chronic pattern of substance use with loss of control, tolerance, dependence, and adverse consequences (Hasin et al. 2013). Another difference between DSM-IV and DSM-5 is the addition of "craving" as a criterion for substance use disorder in DSM-5. In terms of the evidence on the co-occurrence of mood and substance use disorders, these change should make little difference, since the three retained abuse criteria and craving are unidimensional with the seven dependence criteria (all therefore indicating the same underlying condition) and most epidemiological and treatment research on the comorbidity of depression and substance disorders concerned co-occurrence with substance dependence. Further, substance dependence (DSM-IV) and substance use disorder

(DSM-5) are conceptually similar, representing a chronic pattern of substance use with loss of control, tolerance, dependence, and adverse consequences.

In summary, the DSM-5 criteria sets for mood and substance use disorders are similar enough to DSM-IV, and prior criteria that the evidence on co-occurrence described in this chapter can be expected to generalize to the DSM-5 framework. Future research examining co-occurrence of substance and other mental disorders in the DSM-5 framework is needed. Meanwhile in this chapter, evidence described on prevalence and treatment will be derived from studies based on DSM-IV or earlier criteria sets.

117.2.2 Depressive Disorders

117.2.2.1 Major Depressive Disorder

Major depressive disorder represents an episode, lasting 2 weeks or more, of relatively severe depression, characterized by a persistent state, "most of the day, nearly every day" (American Psychiatric Association 2013), of either depressed mood or markedly diminished interest or pleasure in usual activities, or both, along with at least three or four associated symptoms, again occurring nearly every day (anorexia and weight loss, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or low energy, feelings of worthlessness or guilt, trouble concentrating or making decisions, recurrent thoughts of death or suicide). Major depression may occur as a single episode, but in patients, a chronic course is not uncommon, in which there are recurrent major depressive episodes, followed by partial remissions during which some of the depressive symptoms persist.

117.2.2.2 Persistent Depressive Disorder

Persistent depressive disorder (DSM-5), which was called *dysthymia* in DSM-IV, represents a chronic syndrome of depressed mood "more days than not... for at least 2 years" (American Psychiatric Association 2013), along with at least 2 of the following associated symptoms – either low appetite or overeating, insomnia or hypersomnia, fatigue or low energy, low self-esteem, poor concentration or difficulty making decisions, and feelings of hopelessness. Persistent depressive disorder may be specified "with persistent major depression" or "with intermittent major depressive episodes" to indicate the confluence of major depressive episodes with the chronic low-grade symptoms.

117.2.2.3 Prevalence and Co-occurrence of Depressive Disorders with Substance Use Disorders

Like substance use disorders, depressive disorders are among the most commonly occurring mental disorders. Community surveys indicate 10 % or more of individuals have experienced a depressive disorder during their lifetime (Hasin et al. 2005). Depressive disorders are responsible for substantial suffering, functional impairment, lost productivity, and suicide risk. Large community surveys, such as the Epidemiological Catchment Area study (ECA) (Regier et al. 1990), the National Comorbidity

Survey (NCS) (Kessler et al. 1994; Kessler 1995), and the National Epidemiologic Survey on Alcoholism and Related Conditions (NESARC) (Hasin et al. 2005; Grant et al. 2005), consistently show that the presence of a depressive disorder significantly increases the risk of alcohol or drug dependence (or vice versa) by a factor of 2 or more. Treatment-seeking samples tend to display even greater comorbidity due to the relatively greater severity of illness of treatment seekers. Across numerous studies of such samples, the prevalence of major depression has ranged from 15 % to 50 %, making it probably the most common co-occurring psychiatric disorder encountered among drug- or alcohol-dependent patients in treatment (Hasin et al. 2004).

117.2.2.4 Prognostic Effects of Depressive Disorders on Substance Use Disorders

Many longitudinal studies have found that the presence of depression in drug- or alcohol-dependent patients is associated with worse treatment outcome and prognosis. These findings suggest the importance of identifying and treating depression among substance-dependent patients, since the implication is that treatment of the depression has the potential to improve prognosis. Importantly, the findings of the adverse prognosis of depression are most consistent among studies where a depressive disorder (mainly major depression) is diagnosed by clinical history and structured diagnostic assessment. Findings on the association between depression and prognosis of substance use are less consistent when depression is measured only with cross-sectional scales (Hasin et al. 2004). For example, one study that followed alcohol-dependent patients for a year after an index hospitalization found that a diagnosis of major depression was associated with poor drinking outcome over the coming year, while the Hamilton Depression Rating Scale score at baseline was not (Greenfield et al. 1998).

117.2.3 Bipolar Disorders

Bipolar disorders are more rare in the general population, but are more strongly associated with co-occurring substance use disorders. Large community surveys yield estimates of the lifetime prevalence of bipolar I disorder ranging from 1 % to 3 %, another 1 % for bipolar II disorder, and 2 % or more having subthreshold disorders in the bipolar spectrum (Grant et al. 2005; Merikangas et al. 2007). Although bipolar disorders are characterized by the presence of manic or hypomanic episodes during the lifetime, these episodes alternate with episodes of major depression or chronic depression, and the depressed periods typically predominate, particularly later in the course of the illness. Thus, bipolar patients are most likely to present clinically as depressed. When evaluating a depressed, substance-using patient, it is therefore very important to search the history for evidence of past manic or hypomanic episodes because the treatment of bipolar disorders differs significantly from the treatment of depressive disorders. The cornerstone of the treatment of bipolar disorder is mood stabilizer medications – lithium, anticonvulsants, or neuroleptics. Treating bipolar depression with antidepressant medications alone can be ineffective or even cause worsening of mood instability.

117.2.3.1 Bipolar I Disorder

Bipolar I disorder is characterized by the presence of one or more manic episodes over course of the lifetime. Manic episodes are characterized by a week or more of persistently elevated, expansive, or irritable mood, accompanied by at least three associated symptoms, including grandiose thinking, decreased need for sleep, increased talkativeness, racing thoughts, distractibility, increased activity level, and risky or foolish behavior that the person would not usually engage in. The syndrome is severe and causes marked impairment in functioning. Mania may become psychotic with paranoid or grandiose delusions (e.g., a patient becomes convinced that he/she is a messiah or on a special mission from God). Typically, the course of bipolar I includes episodes of major depression, may also include hypomanic episodes, and typically runs a course that is predominated by depressive symptoms.

117.2.3.2 Bipolar II Disorder

Bipolar II disorder is characterized by one or more hypomanic (as opposed to manic) episodes, along with one or more episodes of major depression over the lifetime. A hypomanic episode resembles a manic episode, except that hypomania may be shorter, and is less severe. There must be a change in functioning to meet criteria for hypomania, but hypomania does not cause marked impairment or psychosis. Again, bipolar II frequently runs a predominantly depressive course.

117.2.3.3 Co-occurrence of Bipolar and Substance Use Disorders and Prognostic Effects

Large-scale community surveys indicate that the presence of a bipolar disorder increases the odds of having an alcohol use disorder by a factor of 5 or more and a drug use disorder by a factor of 8 or more (Regier et al. 1990; Kessler et al. 1994; Kessler 1995; Hasin et al. 2005; Grant et al. 2005). In outpatients seeking treatment for substance use disorders, bipolar disorder is less commonly encountered than depressive disorders because bipolar is less frequent in the general population. However, patients with co-occurring bipolar and substance use disorders are particularly likely to be encountered in inpatient settings dealing with more severe dually diagnosed patients.

The co-occurrence of bipolar and substance use disorders is associated with worse outcome for both disorders. Patients with bipolar disorders can be very difficult to manage until the disorder is recognized and successfully treated with mood stabilizers. Conversely, finding the right mood stabilizer regimen for a given patient can be dramatically effective. This, again, suggests the importance, when evaluating substance-dependent patients, of taking a careful past history for past episodes of mania or hypomania.

117.2.4 Co-occurring Depression and Substance Use as a Signal for Other Disorders

A recent analysis of the NESARC data on co-occurrence of mood and substance use disorders yielded an interesting finding (Hasin et al. 2007). When the

association between major depression and substance use disorders is analyzed in such a way as to control for the presence of other disorders (bipolar disorder, anxiety disorders, etc.), the odds ratio of association between depression and substance use disorders is substantially reduced. This suggests that the apparent association between depression and substance use disorders may be explained, at least in part by the presence of the other co-occurring disorders, including anxiety disorders, since anxiety is a commonly occurring symptom among those with depression. In contrast, the association between bipolar disorder and substance use disorders remained significant after controlling for the other disorders. Substance use disorders have high rates of co-occurrence with anxiety disorders, such as panic disorder, social anxiety disorder, and post-traumatic stress disorder (PTSD); attention deficit hyperactivity disorder (ADHD); and personality disorders, including antisocial personality and borderline personality. Each of these disorders, in turn, has high co-occurrence with depressive disorders or symptoms or has symptoms that resemble depression. Thus, in substance-dependent patients, depressive symptoms may be a signal that other disorders are also present. It is therefore important to take a careful history looking, not only for bipolar disorder but also for anxiety disorders, ADHD, or personality disorders. These disorders also have distinct behavioral and pharmacological treatment indications, and instituting appropriate treatment will be important to securing the best clinical outcome.

117.3 Diagnosis of Co-occurring Mood Disorders with Substance Use Disorders

In approaching the differential diagnosis of a patient with a substance use disorder and mood symptoms, it is important to recognize that there are multiple potential relationships between mood symptoms and a substance use disorder. There may be an independent mood disorder (e.g., major depressive disorder or bipolar disorder), or the depressive symptoms may be a manifestation of another co-occurring disorder such as PTSD or ADHD. Mood and substance use disorders may be related by common genetic or environmental risk factors. Stress is the most obvious example of this, as stress is a causal risk factor for both mood disorders and substance use disorders.

Perhaps most commonly, substance use causes mood symptoms, either as part of substance intoxication or withdrawal or as a result of the toxic effects of chronic exposure to substances. Moreover, individuals with substance use disorders often experience negative consequences and losses (e.g., medical problems, loss of employment or family), which may trigger depressive symptoms. Some of these substance-related or substance-induced mood symptoms will resolve if the patient is able to achieve abstinence. Hence, it is almost always appropriate to initiate treatment for a substance use disorder, while sorting out the co-occurring mood disorder. If the patient's substance use is substantially reduced or resolved, the mood symptoms may resolve with it. A number of studies across alcohol- and

drug-dependent samples have shown that initiation of treatment for substance use disorders and achievement of abstinence are associated with marked improvement in mood symptoms (Brown and Schuckit 1988; Weddington et al. 1990; Strain et al. 1991; Satel et al. 1991; Brown et al. 1995; Liappas et al. 2002).

It is also important to bear in mind that resolution of a depressive syndrome with treatment of the substance abuse alone is not pathognomonic of a substance-induced depression. Depressive disorders, particularly in the mild to moderate range of severity, respond well to psychotherapy, such as cognitive behavioral therapy (CBT) or interpersonal therapy (IPT). Treatment for substance use disorders generally includes nonspecific psychotherapeutic elements, such as development of a supportive clinician-patient relationship and treatment alliance, which are likely to be helpful with treating depression. Further, many treatments for substance use disorders include components on coping with stress and with dysphoric moods that are quite similar to cognitive behavioral techniques for treating mood and anxiety disorders. Further, reductions in substance abuse and related problems in response to treatment are likely to reduce stress and improve self-efficacy, also likely to help depression. In summary, good treatment for substance use disorders may also be effective for treatment of an independent depressive disorder.

117.3.1 DSM-IV/DSM-5 Approach to Co-occurring Mood and Substance Use Disorders

Before the advent of DSM-IV, there was not a clear consensus on how to diagnose co-occurring mood disorders in the setting of substance use disorders. There was recognition that some co-occurring mood disorders were independent of substance use and some mood syndromes were caused by substance use, which would resolve once abstinence was achieved. However, determining the optimal way to handle the large proportion of cases, in which the history is not so clear with respect to relative onset and offset, is less obvious, especially when the patient does not quickly achieve abstinence. DSM-IV advanced the field by distinguishing between independent mood disorders, substance-induced mood disorders, and mood symptoms that are usual effects of substances and for providing some criteria to make the distinctions. DSM-5 has retained this system. Substance-induced mood disorder provides a category in which to place the unclear cases, in which a mood disorder syndrome exceeds the symptoms that would be expected from intoxication and withdrawal, but the syndrome has not occurred in the absence of regular substance use. It has generated meaningful research as to its prognosis and course, as reviewed below.

117.3.1.1 Independent Mood Disorder

An independent mood disorder is diagnosed if the patient meets full criteria for the mood disorder (e.g., major depression, persistent depressive disorder, bipolar I) and the symptoms can be established by history to be temporally independent of substance abuse (prior onset or emergence or persistence during periods of

abstinence). DSM-IV also suggested that an independent disorder could be diagnosed if its symptoms were substantially in excess of effects expected to be caused by the substance(s) the patient was taking. DSM-5 deals with this by specifying that a substance-induced disorder is only diagnosed if the mood syndrome and symptoms are consistent with symptoms known to be caused by the substance(s). The clinical implications are similar. In the criteria sets for substance-induced mood disorders, DSM-5 suggests that a mood syndrome co-occurring with substance use may be considered an independent disorder (and thus distinguished from substance-induced disorder) if the mood syndrome had its onset prior to the onset of substance abuse, or persists for about 1 month or more after abstinence is achieved, or there is a clear past history of independent mood disorder episodes. An example might be a current major depression syndrome that had its onset concurrent with substance abuse in the current episode, but there is a clear history of one or more major depressive episodes during past abstinent periods.

117.3.1.2 Substance-Induced Mood Disorder

A substance-induced mood disorder is diagnosed if there is a "persistent disturbance in mood," which (a) develops at or soon after substance intoxication or withdrawal and (b) the substance(s) in question is "capable of producing the symptoms," and the syndrome is not better explained by a diagnosis of an independent mood disorder. There must be significant distress or impairment. Further, with respect to distinguishing a substance-induced mood disorder from usual effects of substances, the DSM-5 criteria state that a substance-induced mood disorder should be diagnosed, instead of a diagnosis of substance intoxication or withdrawal, only if "the mood symptoms predominate and are sufficiently severe to warrant clinical attention." DSM-IV worded this slightly differently, indicating that substance-induced mood disorder should be diagnosed when the mood and related symptoms (e.g., insomnia) exceed what would be the expected effects of intoxication or withdrawal and warrant clinical attention. Again, the clinical implications are similar.

117.3.1.3 Usual Effects of Substances

Mood symptoms, such as depressed mood, insomnia, and weight loss, can also be usual effects of substance intoxication or withdrawal. DSM-IV and DSM-V contain detailed criteria sets for the intoxication and withdrawal syndromes of alcohol, nicotine, and each of the other commonly abused drugs. Clinicians should be mindful of these lists of symptoms when evaluating patients with co-occurring mood symptoms and substance use. These symptoms have various time frames, but generally, symptoms of intoxication last only for the few hours during and after substance ingestion while blood levels are peaking and before they substantially decrease. Symptoms of withdrawal usually evolve and resolve over a period of a few days. Subacute withdrawal syndromes (also called protracted withdrawal), sometimes lasting a few weeks, have been described, particularly for alcohol and opioid dependence, although boundaries between this phenomenon and substance-induced disorders can be difficult to define.

Depressed mood and related symptoms (e.g., anxiety, fatigue, hypersomnia, insomnia, difficulty concentrating, irritability) occur variously as part of the withdrawal syndromes of most of the common addictive substances. In summary, when conducting a diagnostic evaluation on a substance-using patient, familiarity with the intoxication and withdrawal effects of the substance(s) involved is important in order to distinguish mood symptoms that are best explained as components of intoxication or withdrawal from symptoms that are better explained as a substance-induced disorder.

117.3.1.4 Co-occurring Bipolar and Substance Use Disorder

Episodes of frank mania are generally too persistent (1 week or more) and too severe to be explained as substance induced. For example, cocaine or methamphetamine intoxication may produce a syndrome closely resembling mania (increased activity, hyper-loquaciousness, grandiosity, lack of need for sleep, and psychosis with paranoid or grandiose delusions), but this typically only lasts for the duration of the drug binge, a day at most, after which there will be a crash with the typical depressive withdrawal symptoms (fatigue, hypersomnia, depressed mood, etc.). Hence, a history of one or more episodes of frank mania in a patient presenting with co-occurring mood symptoms and substance problems is clear evidence of co-occurring independent bipolar disorder that requires appropriate mood stabilizer medication.

Hypomania can be more difficult to identify both in the present and historically. Hypomania is milder, and patients may not report it because they do not remember it or did not experience it as a departure from normal functioning. Moreover, periods of elevated mood, and increased energy and activity, may be difficult to distinguish from periods of normal mood – for example, when a chronically depressed patient becomes euthymic or when a patient has an exciting life event such as a new job or another major success. Periods of hypomania can be difficult to distinguish in a patient with heavy stimulant use, given the shorter duration of hypomania and the overlap in symptoms between hypomania and cocaine or stimulant intoxication (e.g., euphoria, increased sociability). As with depressive disorders, to confirm an independent bipolar II disorder, it becomes important to seek episodes in the history in which syndromes of hypomania occurred in the absence of stimulant-like substances.

117.3.2 Course and Prognosis of DSM-IV Independent and Substance-Induced Depression

Prior to DSM-IV, considerable evidence existed that independent depressive disorders could be identified with distinct prognostic and treatment implications. Brown and Schuckit showed among hospitalized alcoholics that a history of major depression prior to the onset of alcohol problems over the patient's lifetime (primary depression) was associated with depressive symptoms that persisted despite 3–4 weeks of abstinence (Brown and Schuckit 1988; Brown et al. 1995).

Rounsaville and colleagues, using the Schedule for Affective Disorder and Schizophrenia, a structured diagnostic instrument, found major depression to be associated with worse prognosis among drug-dependent patients (Rounsaville et al. 1982, 1986; Carroll et al. 1993). We and others found that depression with evidence of temporal independence from substance use either by history (Nunes et al. 1993, 1998; McGrath et al. 1996) or through observed persistence of depression symptoms during abstinence (Mason et al. 1996; Cornelius et al. 1997; Roy 1998) responded to antidepressant medication.

117.3.2.1 Structured Diagnostic Assessment

With the advent of DSM-IV, the Structured Clinical Interview for DSM-IV (SCID) incorporated a module for substance-induced mood disorder and logic for diagnosing a mood syndrome as independent or substance induced. However, the determinations were left largely up to clinical judgment with little guidance in the interview as to how to make the distinction. The Psychiatric Research Interview for Substance and Mental Disorders (PRISM) (Hasin et al. 2006) was developed to operationalize the diagnosis of co-occurring substance and other mental disorders within the DSM-IV framework. For a given syndrome, such as major depression, the interviewer is asked, for each criterion symptom, to judge whether that symptom appears attributable to usual effects of substances. The substances that might cause that symptom, either as intoxication or withdrawal effects, are listed. For example, when a depressed patient reports insomnia, the interviewer is asked to determine whether substances that might cause insomnia (stimulant intoxication or alcohol, sedative, or opioid withdrawal) could explain the insomnia. The insomnia is only scored as positive, and allowed to contribute to a diagnosis of a depressive disorder, if it can be determined either not related to or exceeding the expected effects of the substances the patient is taking. If sufficient criteria are endorsed to allow diagnosis of a depressive syndrome, then the interviewer is asked to determine whether the depressive syndrome is temporally independent of current substance use in terms of its onset and persistence during abstinence. If the history indicates that the depressive episode started prior to the onset of substance use or persists during a substantial abstinent period (e.g., a month or more), then it is diagnosed as independent. Otherwise, it is diagnosed as substance induced.

Thus, the PRISM provides an operationalized definition of substance-induced depression that is quite stringent. It requires criteria for a full depressive syndrome (e.g., for major depression) to be met, and it requires that the symptoms contributing to that syndrome not be better explained as toxic or withdrawal effects. In contrast, DSM-IV criteria for substance-induced depression refer only to a syndrome of depression without specifying how many or which symptoms of depression need to be present. DSM-5 criteria for substance-induced depression similarly require that there be a persistent disturbance in mood or loss of interest (much like the essential two criteria for major depression) but no specific associated features (such as insomnia, fatigue, suicidal ideation). This highlights an area of vagueness in the DSM-IV and DSM-5 definitions of substance-induced disorders, which the PRISM sought to correct by being more definitive. The PRISM yields

a diagnosis of substance-induced major depression, rather than the more broad and vague category of substance-induced depression.

117.3.2.2 Prognostic Effects

Subsequent research with the PRISM established good to excellent reliability of diagnoses of independent and substance-induced major depression (Hasin et al. 2006). Further, there were clear prognostic effects. In a longitudinal study, substance-dependent patients entering an inpatient treatment facility were diagnosed with the PRISM while hospitalized, then followed for 1 year after discharge. Substance-induced major depression was found to predict failure to achieve abstinence after discharge from hospital, while independent major depression was found to predict relapse to substance use after periods of abstinence (Hasin et al. 2002; Samet et al. 2013). Both independent and substance-induced depression were associated with suicidal ideation (Aharonovich et al. 2002). Further, over half of cases diagnosed as substance-induced depression at baseline converted into an independent depression over the year's follow-up, based on the major depression persisting during a period of at least a month of abstinence (Nunes et al. 2006). Predictors of conversion to independent depression included a past history of an independent major depression and either PTSD or borderline personality disorder (Nunes et al. 2006), again suggesting the importance of identifying other disorders that commonly co-occur with both mood and substance use disorders. Studies with other samples and diagnostic methods have similarly suggested the validity and prognostic significance of independent and substance-induced depressive disorders as conceptualized by DSM-IV/DSM-5 (Schuckit et al. 1997; Ries et al. 2001, 2008) and the finding that a substantial proportion of substance-induced depression will convert to an independent depressive disorder over time (Ramsey et al. 2004).

117.3.2.3 A Note About Terminology

The term "substance-induced depression" carries a causal implication, namely, that the substances are definitely causing the observed depression syndrome. This can cause clinicians to underestimate the potential clinical significance of a substance-induced depression, both because intoxication and withdrawal effects are also induced by substances and also because, as reviewed above, some depressions diagnosed as "substance induced" will turn out to be independent depressions if followed into a period of abstinence. Substance induced is to some extent a holding category for depressions for which the status as independent is uncertain at the time of diagnosis. It might be useful for clinicians to think of this as "substance induced until proven otherwise," to emphasize that continued clinical attention is warranted and that the depression may turn out to be independent or to warrant specific treatment.

In summary, these studies suggest that in diagnosing a substance-induced depression, it is important to determine what depressive syndrome is being observed – e.g., substance-induced major depression. The findings suggest that substance-induced depression is a valid and useful category. It represents a diagnostic entity that lies between usual toxic effects of substances and an

independent mood disorder. As the DSM-IV and DSM-5 criteria suggest, substance-induced depression "warrants clinical attention" because it carries adverse prognostic effects (suicidal ideation, lower likelihood of achieving abstinence) and is likely to convert to an independent depression over time. Further, as the DSM-5 criteria suggest, a past history of independent depression may be considered sufficient evidence to diagnose a current depression as independent, rather than substance induced. Other co-occurring disorders such as PTSD should also be suspected.

117.3.3 Summary and Recommendations for Diagnostic Assessment

117.3.3.1 Screening Instruments

Instruments that assess cross-sectional mood symptoms (e.g., Beck Depression Inventory, Hamilton Depression Rating Scale, Brief Symptom Inventory, or Quick Inventory of Depressive Symptomatology – Self-Report (QIDS-SR)) are useful for screening. However, by themselves they do not indicate the presence of any specific mood disorder and have unclear prognostic or treatment implications.

117.3.3.2 Clinical History and DSM-IV/DSM-5 Criteria

A substance-dependent patient with mood symptoms should be evaluated by taking a careful lifetime clinical history. The history should seek to establish the onset of substance use disorders over the lifetime and substantial periods of abstinence lasting a month or more. The history should then establish the onset and course of mood syndromes (major depressive episodes, persistent depressive disorder, mania, hypomania), in the context of the lifetime course of substance use, and apply the DSM-5 criteria for independent or substance-induced disorders. Among other things, this means establishing that symptoms of a mood disorder are not better explained as usual effects of substances or exceed what would be expected from the usual effects of substances. A mood disorder that cannot be established to be temporally independent of substance abuse, but exceeds the expected effects of substances, is diagnosed as substance induced. For substance-induced syndromes, we also recommend noting the full syndrome that is in evidence, for example, "substance-induced major depression" if the full criteria for major depression are met (i.e., five or more criteria are met), as some of the stronger prognostic data pertain to substance-induced depression defined in this way (Hasin et al. 2002; Aharonovich et al. 2002; Nunes et al. 2006; Samet et al. 2013).

117.3.3.3 Search the History for Mania or Hypomania

The presence of one or more episodes of mania and hypomania indicates a bipolar disorder, which carries prognostic and treatment implications distinct from depression. Mania and hypomania may be difficult to elicit in the history. It is often helpful to interview family members, who may recall such episodes when the patient does not.

117.3.3.4 Look for Other Co-occurring Disorders

We also recommend a thorough review of the history for other disorders that commonly co-occur with mood disorders, including PTSD, social anxiety disorder, and other anxiety disorders; ADHD; and borderline personality. The presence of mood symptoms may signal the presence of one of these disorders. Such disorders have symptom patterns that are distinct from typical substance effects – substance use does not cause phobias, social anxiety, or reexperiencing symptoms of PTSD. Some have clear childhood onset (e.g., ADHD, social anxiety disorder), well prior to the onset of substance problems. And they have distinct treatment indications for both behavioral therapy and medications.

117.4 Treatment of Co-occurring Mood Disorders

117.4.1 Depressive Disorders

117.4.1.1 Antidepressant Medications

A number of placebo-controlled trials have examined the effect of antidepressant medication on mood and substance use outcome among substance-dependent patients with diagnosed mood disorders. Two meta-analyses (Nunes and Levin 2004; Torrens et al. 2005), published 10 years ago, reached similar conclusions, namely, that antidepressant medications are useful in improving both mood outcome and substance use outcome; these findings are more clear among alcohol-dependent patients. Among drug-dependent patients, there are fewer studies with less clear results. More recent studies have been mixed, with some negative trials (Gual et al. 2003; Kranzler et al. 2006; Cornelius et al. 2009; Raby et al. 2014). These include a large trial among alcohol-dependent outpatients that showed a high placebo response rate and no medication effect on mood or substance use outcome, despite patients being diagnosed with independent major depression using the PRISM. Other more recent trials have also been positive, at least in showing a beneficial effect of antidepressant medication on mood outcome (Hernandez-Avila et al. 2004; McDowell et al. 2005; Riggs et al. 2007).

117.4.1.2 Placebo Response and Other Factors Associated with Response to Antidepressants

A striking finding from the antidepressant trials is the wide variation in placebo response among studies, which varies from 20 % to more than 70 %, and the strong relationship between placebo response and study outcome. Studies with low placebo response tended to show beneficial effects of antidepressant medication on mood and substance use outcome, while studies with high placebo response showed no benefits of medication, a pattern observed in the original meta-analysis (Nunes and Levin 2004) and evident in the more recent studies (Gual et al. 2003; Kranzler et al. 2006; Cornelius et al. 2009; Raby et al. 2014; Hernandez-Avila et al. 2004; McDowell et al. 2005; Riggs et al. 2007). Several other study features were also found to be related to low placebo response and to benefit of medication, including

Table 117.1 Factors associated with low placebo response and beneficial effect of antidepressant medication in placebo-controlled trials among depressed, substance-dependent patients

Factor associated with low placebo response and medication efficacy	Potential mechanism	Implications for clinical management
Abstinence established before diagnosing depression	Withdrawal effects and substance-induced depression resolve with abstinence, leaving independent depressions more likely to benefit from medication	Initiate treatment with hospitalization for severely ill patients or evidence-based psychosocial treatment (e.g., cognitive behavioral relapse prevention). Some depression will resolve. Depression that persists should be considered for antidepressant medication
Diagnosis of a depressive disorder, rather than merely depressive symptoms	Depressive symptoms are more likely to represent withdrawal effects or be substance induced	Base diagnosis of depression on careful clinical history and application of DSM-IV/DSM-5 criteria for independent or substance-induced depression
Noradrenergic or mixed-mechanism antidepressants	Less evidence of efficacy for serotonin reuptake inhibitors (SRI) among substance-dependent patients may relate to the study samples (high placebo response) rather than lack of efficacy. However, several trials suggest SRI makes drinking worse among early onset alcoholics	SRIs may still be considered the first-line treatment based on their good safety and tolerability, but consider switching to a noradrenergic or mixed-mechanism medication (e.g., venlafaxine, duloxetine, mirtazapine, nefazodone) if non-responsive to SRI
Concurrent manual-guided behavioral intervention	Behavioral interventions for substance use disorders (e.g., cognitive behavioral relapse prevention) typically contain elements likely to help with depression (e.g., support, coping skills)	Initiate psychosocial treatment for the substance use disorder as a first step

(a) diagnosis of depression after abstinence has been established, particularly enforced abstinence on an inpatient unit; (b) diagnosis of a depressive disorder, as opposed to merely depressive symptoms; (c) noradrenergic or mixed-mechanism antidepressants (serotonin reuptake inhibitors have shown little evidence of efficacy); and (d) concurrent manual-guided psychosocial intervention (psychosocial interventions were associated with high placebo response and absence of benefit of medication). These are described further in Table 117.1 along with their possible mechanisms and implications for clinical practice.

The phenomenon of high placebo response is not surprising, given the evidence from the wider literature on treatment of depression, which shows cognitive

behavioral and other psychosocial interventions to be effective and shows high placebo response, particularly among patients with only mild to moderate depressive symptoms. Generally, the level of severity of depression in clinical trials needs to be high (severe) before there is consistent evidence that antidepressant medication is superior to placebo (Fournier et al. 2010). For the treatment of substance-dependent patients with depression, then, a reasonable first step is to initiate treatment for the substance use disorder. For more severely depressed or substance-dependent patients, hospitalization may be needed to induce abstinence. Or, on an outpatient basis, evidence-based behavioral treatment for the addiction can be offered. If the depression fails to respond once addiction treatment is initiated, then specific antidepressant treatment should be considered.

117.4.1.3 Behavioral Treatments

As noted above, manual-guided psychosocial treatments for substance use disorders are associated with high placebo response rates in the antidepressant medication trials, suggesting these interventions have some efficacy at treating depression in this population. Some controlled trials have examined cognitive behavioral treatments for depression among substance-dependent patients, with some evidence of efficacy (Brown et al. 1997, 2001; Patten et al. 1998; Carpenter et al. 2006, 2008; Daughters et al. 2008; Hides et al. 2010). Psychosocial and behavioral treatments have solid evidence of efficacy for treatment of mood and anxiety disorders, and their use avoids risks of drug interactions that may be of concern when prescribing antidepressant medications to substance-dependent patients. Thus, such behavioral interventions may be considered as a first step, prior to medication, particularly when the severity of depression is in the mild to moderate range.

117.4.1.4 Treatment of the Substance Use Disorder

Again, it bears emphasizing that when a patient presents with combined substance use and mood disorders, treatment should begin by identifying the substance as problem and initiating treatment for the substance use disorder. This could range from brief motivational intervention to a more formal treatment regimen. Successful treatment of the substance use disorder, with resultant reduction in substance use or abstinence, eliminates the toxic effects the substance may likely be having on the nervous system and is likely to improve or even eliminate symptoms of depression (Brown and Schuckit 1988; Weddington et al. 1990; Strain et al. 1991; Satel et al. 1991; Brown et al. 1995; Liappas et al. 2002). That said, when a depressive disorder persists after initiation of treatment for the addiction, specific antidepressant treatment, either behavioral, medication, or a combination of the two, should be initiated.

117.4.1.5 Combined Medications for Depression and Substance Use

There have been a few studies of medications for treatment of addictions, such as disulfiram and naltrexone (Petrakis et al. 2005, 2007), buprenorphine, or methadone (Strain et al. 1991; Nunes et al. 1998), among patients with substance and mood or

anxiety disorders or symptoms. These studies suggest such medications are at least well tolerated and potentially effective at improving mood symptoms, probably because they are effective in reducing or eliminating substance use.

One innovative study examined the combination of sertraline and naltrexone for alcohol-dependent patients with depression, finding the combination superior to either medication alone or placebo (Pettinati et al. 2010). Medications for treating substance use disorders are generally underutilized and should be always considered as part of treatment planning generally, as well as specific treatment planning for patients with combined mood and substance use disorders.

117.4.2 Bipolar Disorders

Thorough reviews of medication treatments of bipolar disorder can be found in published reviews elsewhere (Suppes et al. 2005; Thase 2007), and treatment of bipolar disorders in the setting of substance use disorders is covered in detail in a separate chapter of this text. Briefly, lithium, anticonvulsants (e.g., valproate, carbamazepine, lamotrigine), and neuroleptics (particularly second-generation agents such as quetiapine, risperidone, and aripiprazole) are the mainstays of treatment for bipolar disorder. Among these, lithium (Geller et al. 1998) and valproate (Salloum et al. 2005) have been tested in controlled trials and found effective for patients with co-occurring bipolar and substance use disorders. Despite the typical predominance of depressive symptoms and syndromes among bipolar patients, antidepressant medications are often ineffective or even counterproductive among bipolar patients. This again highlights the importance of making the differential diagnosis between bipolar and depressive disorders with the clinical history.

Behavioral treatments can also be helpful as adjuncts to medication treatment for bipolar disorder by building treatment alliance, medication adherence, and coping skills (Craighead and Miklowitz 2000; Scott and Gutierrez 2004). Weiss and colleagues have developed a group behavioral treatment for patients with combined bipolar and substance use disorders, integrated group therapy (IGT), which has shown evidence of efficacy in a series of controlled trials (Weiss 2004; Weiss et al. 2007, 2009; Weiss and Connery 2011). Interestingly, among its key features, IGT encourages patients to think of their combined mood and substance problems as a single disorder ("bipolar substance abuse"). This stands in contrast to the DSM approach, reviewed above, which involves establishing separate mood and substance use disorder diagnoses. It suggests that a co-occurring mood and substance use disorder may be more than the sum of the separate diagnoses and best treated in an integrated fashion.

117.5 Conclusion

As we hope this chapter has illustrated, considerable evidence has accumulated that mood disorders can be distinguished from substance-related syndromes and

effectively treated, through a careful clinical history, and longitudinal observation of the response of mood symptoms and substance use as treatment is implemented. A guideline exists for the differential diagnosis of independent versus substance-induced mood disorders versus intoxication or withdrawal effects of substances, based on DSM-IV/DSM-5 criteria. In all cases, it makes sense to initiate treatment of the substance use disorder as a first step. Substance-induced depression, and even cases that meet criteria for an independent depressive disorder, may respond to behavioral treatment for the substance use disorder. However, for cases that do not respond, specific antidepressant treatment should be considered – either medication or behavioral treatment or both. It has been shown that many cases of substance-induced depression, particularly if a full major depressive syndrome is present, will be observed to persist during abstinence over follow-up, thus converting to independent depression. For clear-cut or severe cases of major depression, initiation of antidepressant treatment may be considered concurrent with substance abuse treatment from the outset. A careful search of the history should be conducted for episodes of mania or hypomania, indicating the presence of bipolar disorder. Bipolar disorder should generally be treated with mood-stabilizing medications concurrent with the initiation of treatment for the substance use disorder.

In the treatment of mood disorders, the variety of treatment options has led to the development of and testing of treatment algorithms that outline potential sequences of treatments to be followed depending on the response to prior treatments (Crismon et al. 1999; Trivedi et al. 2004; Davis et al. 2007). The various treatment options for co-occurring substance and mood disorders (behavioral and medication treatments for substance use disorders, medication and behavioral treatments for mood disorders) suggest that similar algorithms might be developed and tested.

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Bipolar Disorders and Co-Occurring Addictions

118

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Abstract

Several studies have provided evidence that patients with bipolar disorder (BD) show high prevalence of a comorbid substance use disorder (47–60 %) (SUD). The cause of the high comorbidity rate between BD and SUD has not been clearly established; the relationship is probably bidirectional. This combination of entities is characterized by frequent relapses, suicide attempts, elevated impulsivity, and greater frequency of rapid cycles, more severe picture, complicated diagnosis, poor adherence, and poor response to treatment. Patients who suffer this dual diagnosis have worse clinical course. The substances that were most frequently associated to SUD were alcohol, nicotine, and cocaine. Patients with BD should be warned about the risk of developing an SUD and about the importance of its early detection. Different pharmacotherapies have been studied in open and non-blind studies and in small groups and in same well-controlled trials in which patients whose mood disorder had been stabilized were treated with a double-blind medication. In these studies, adding a medication to reduce substance use to a pharmacotherapy for treating bipolar disorder did not consistently reduce substance use in this patient group. Antiseizure agents are profiled as the most promising treatments. In addition, there is an increase in the use of atypical antipsychotics, although there are few double-blind, controlled studies and the role of the adjuvant therapy for SUD must still be evaluated.

118.1 Introduction

Psychiatric disorders and substance use disorders (SUD) commonly co-occur. The term dual diagnosis or dual pathology is commonly used to refer to the concomitant presentation of a SUD and another mental disorder (Szerman et al. 2013). There is a high prevalence of dual disorders in drug-dependent patients seeking treatment, (Szerman Bolotner et al. 2011; Roncero et al. 2011; Szerman et al. 2012).

The prevalence of bipolar disorders (BD), using the most extensive definition of this disease (bipolar spectrum), would be between 5 % and 7 % of the general population (Akiskal et al. 2000). In relationship with the dual diagnosis associated to this disorder, it has already been described in several studies. Population-based studies have provided documentation that patients with bipolar disorder show the highest prevalence of comorbid SUD. Bipolar I subjects appear to have higher rates of these comorbid conditions than bipolar II subjects (Chengappa et al. 2000).

In the Epidemiologic Catchment Area Survey (ECA), 60.7 % of the subjects with type I bipolar disorder had a comorbid SUD. This percentage exceeds that of any other psychiatric disorder, including type II bipolar disorder that also has an equally high comorbidity (Regier et al. 1990), and is only exceeded by antisocial personality disorder. These comorbidity rates significantly increase if the most benign and mild cases of BD or cyclothymic disorder that often occur subclinically or with subthreshold symptoms are taken into account.

In the National Epidemiologic Survey on Alcoholism and Related Conditions, which surveyed 43,093 people in 2001 and 2002 (Hasin et al. 2007), and in and the National Comorbidity Survey Replication, which surveyed 9,282 people in 2001 and 2003 (Kessler et al. 2005; Merikangas et al. 2007), comorbidity of mental disorders and SUD was evaluated. The lifetime prevalence of bipolar spectrum disorders (bipolar I and II disorders and subthreshold bipolar disorder) is estimated to be approximately 4.4 %. Based on distributions of age at onset, the projected lifetime risk at age 75 is higher, with estimates of 5.1 % for bipolar I and II disorders. Comorbidity of these disorders with SUD is substantially greater. The lifetime prevalence rate of any BD and any substance use disorder is 47.3 % and for bipolar I disorder and any substance use disorder is 60.3 %.

118.2 Clinical Features

The cause of the high comorbidity rate between BD and SUD has not been clearly established; the relationship is probably bidirectional (Tohen et al. 1998) and based on neurobiological facts (Szerman et al. 2013). A different hypothesis has been proposed, among which impulsivity, considered by different authors as an underlying psychopathology dimension in all the periods of bipolar disease (Swann et al. 2001), is one of the most relevant. Impulsivity is also identified as a primordial factor in SUD. Furthermore, both disorders, BD and SUD, could represent manifestations of a single genetic diathesis (Winokur et al. 1995). Other explanation for this dual disorder is the "self-medication hypothesis", which states that some patients experience improvement in psychiatric symptoms as a result of substance use (Weiss et al. 2004).

BD may occur, and in fact often do, comorbidly with SUD and are generally, in the clinical practice, considered, diagnosed, and treated exclusively as substance abuse or dependence, overlooking the presence of the affective disorder, which reduces diagnostic and therapeutic possibilities (Merikangas et al. 2007). This indicates why it has clinical and health care importance.

Clinical management of this patient has been described as a highly complicated process (Roncero et al. 2009) (Table 118.1). Patients who suffer this dual diagnosis have worse clinical course; tend to have greater chronicity of both comorbid disorders (Kranzler et al. 1996; Goldberg et al. 1999); have symptoms that are

Table 118.1 Clinical features in dual-bipolar patients

Clinical	Greater chronicity
	Risk suicide
	Greater frequency of rapid cycles
	More severe picture
Treatment	Complicated diagnosis
	Poor adherence
	Difficult managing
	Greater frequency of hospitalization

more difficult to treat, such as those of the mixed affective type; and finally have greater frequency of rapid cycles and hospitalization (Casas et al. 2008). On the other hand, these patients have an increased risk of suicide during their lifetime in comparison with BD patients without substance abuse or dependence (39.5 % versus 23.8 %, respectively) (Dalton et al. 2003).

The presence of comorbid SUD makes it difficult to achieve clinical stabilization of the bipolar patient and also significantly worsens their global functioning (Weiss et al. 2005). Patients who present BD and SUD comorbidly develop a more severe picture (with anxiety, mixed or dysphoric mania, and rapid cycles) than patients who only have BD (Feinman and Dunner 1996). Regarding the severity of the symptoms, BD is less severe in patients who begin with alcohol abuse or dependence and then develop BD than in those who begin with BD. In addition, the former tend to recover faster (Winokur et al. 1995; Strakowski et al. 2005).

Patients with BD should be warned about the risk of developing an SUD and about the importance of its early detection (Brady and Sonne 1995; Casas et al. 2008). Prevention and treatment of the substance use disorder is especially indicated for patients with an early age at onset of a BD (Pettinati et al. 2013).

Gender differences have been studied in dual-bipolar disorders. More symptoms and episodes of depression have been reported among women; however, there is no conclusive evidence for gender differences. Further studies should be made (Miquel et al. 2011).

The substances that were most frequently associated to SUD were alcohol, nicotine, and cocaine (Casas et al. 2008). Drug use in depressed or manic episode was studied by Maremmani and cols. who described that stimulant use was more prevalent during the "up" rather than the "down" phase of the illness. As well, patients with a depressive episode more frequently used nonprescribed anxiolytic-hypnotics. Bipolar patients were found to use cocaine-amphetamines more frequently during a hypomanic episode, whereas the use of cannabis and cocaine-amphetamines occurred more frequently during a manic episode. The associated use of alcohol, cocaine-amphetamines and cannabinoids was more frequently encountered during a mixed episode (Maremmani et al. 2012).

118.2.1 Diagnosis

Diagnosis of dual-bipolar patients is a very complex process. As it is known, use of certain stimulant substances may cause symptoms that are not differentiated from mania or hypomania during the time that the drug has a pharmacological effect. All the aforementioned facts underscore the importance of an accurate and complete diagnostic evaluation of this dual diagnosis and of performing an individualized treatment, considering all the comorbid disorders, their interrelationships, and prognostic implications (Krishnan 2005) with the final objective of achieving a treatment in these patients that would provide.

Self-administered questionnaires may be a valid instrument for the detection of substance abuse in BD patients (Weiss et al. 1998a). However, BD questionnaires should be used with caution in patients being treated for SUD (Nallet et al. 2013).

For the diagnosis of dual-bipolar patients, the following are recommended (Casas et al. 2008):

- Two weeks may be necessary to rule out the chance of a manic episode in a patient with SUD (with or without background of BD) being induced or provoked by the effect of the drugs, and the evaluation of such episode in patients with BD and SUD should be done using the usual instruments aimed at patients with BD for mania.
- In patients with SUD without a background of BD and who have episodes of depression/mania, the possible previous symptoms of hypomania should be reevaluated since these may have been interpreted as secondary to the SUD.
- Special care must be taken when examining patients with alcohol abuse since this may often mask a diagnosis of concomitant BD.

118.2.2 Treatment

Patients with co-occurring bipolar and SUD are a difficult-to-treat population, and conducting research with this group can be particularly challenging. Integral treatment of the dual patient requires both a psychopharmacological and psychotherapeutic approach. Typically, these patients are treated for either their mood disorder or their SUD before receiving treatment for the other disorder (Nunes et al. 2010). However, the experts recommend that if a concomitant SUD is detected in the common clinical practice, both treatments are administered simultaneously, without giving priority of one over the other (Casas et al. 2008).

In patients with uncontrolled SUD and personal background of BD, hospital admission is frequently required. As well, more frequent visits have been proposed (one every 2 week), and when there is a suicide attempt, admission of the patient is especially recommended (Casas et al. 2008).

118.2.3 Drug Treatment

Overall, findings from the relatively small amount of available data indicate that pharmacotherapy for managing mood symptoms can be effective in patients with SUD, although results have not been consistent across all studies (Pettinati et al. 2013).

There is a paucity of pharmacotherapy research focused exclusively on patients with dual-bipolar disorder. Medication trials have typically excluded individuals with BD with comorbid SUD. In regard to treatment with drug agents, there is abundant bibliography regarding the use of lithium and valproate in dual diagnosis, especially with alcohol abuse. However, patients who were prescribed both lithium

Table 118.2 Double-blind clinical placebo-controlled trials in dual-bipolar patients

Author	Dependence	Add-on treatment	Mood	SUD result
Salloum et al. 2005	Alcohol	Valproate	None	Reduce drinking
Brown et al. 2008	Alcohol	Quetiapine	None	None
Brown et al. 2009	Alcohol	Naltrexone	None	None
Stedman et al. 2010	Alcohol	Quetiapine	Reduction of depressive symptoms	None
Tolliver et al. 2012	Alcohol	Acamprosate	None	None
Brown et al. 2007	Cocaine	Citicoline	None	Reduce cocaine use

and valproate were more likely to report full compliance with valproate than with lithium (Weiss et al. 1998b). Furthermore, in dual-bipolar patients, lithium administration has been reported as a high risk of interactions with opiate agonists and/or treatments for concurrent medical conditions (Roncero et al. 2009). On the other hand, antiepileptics do not induce counter-polar states (depressed patients abruptly turning manic or hypomanic or patients currently hypomanic or manic abruptly turning depressed), so their use among these patients has been proposed (Maremmani et al. 2010). Equally, a literature and series of studies, although with unequal results, are found in relationship to the use of carbamazepine, gabapentin, topiramate, lamotrigine, and atypical antipsychotics, among others. Antidepressant should be prescribed with caution in order to avoid inducing a manic episode. SSRI (always associated with mood stabilizer) could be the more adequate treatment for a depressive episode (Casas et al. 2008).

However, in the last years, at least six principal double-blind placebo-controlled trials published have targeted dual-bipolar adults. Alcohol was the primary substance in five of the six trials, and the remaining study focused on cocaine use. The typical research paradigm for studying pharmacotherapy in these trials was to give a double-blind medication, primarily to treat the SUD after the patient was stabilized on a medication for the BD (Pettinati et al. 2013). Thus, the few published double-blind placebo-controlled trials have "added on" other medications that sometimes were a treatment for BD, valproate (Salloum et al. 2005) or quetiapine (Brown et al. 2008; Stedman et al. 2010) or a medication for treating alcohol dependence (naltrexone (Brown et al. 2009) or acamprosate (Tolliver et al. 2012)) or a nutritional supplement (citicoline (Brown et al. 2007)) (Table 118.2).

Typically, the double-blind clinical trials not only evaluated the medication's efficacy compared with placebo in reducing substance use but also assessed any further reduction in mood symptoms that the double-blind medication might provide beyond any medication patients were taking for their mood disorder. This type of design has its limitations, and it does not allow the flexibility needed to evaluate investigative medications for mood and addiction outcomes independently of other medications the patient is already taking to treat the mood disorder (Pettinati et al. 2013).

Results of the majority of the trials revealed that no additional benefit was achieved in reducing either depressive or manic symptoms. However, failure to show a differential response to depression in bipolar patients should not be surprising given the study design that is being used. Two trials showed a significant reduction in substance use: one using valproate to reduce drinking (Salloum et al. 2008) and the other using citicoline to reduce cocaine use (Brown et al. 2007). There are other trials in which bipolar patients were a minority in the study group or in which outcomes were indistinguishable from those of other types of patients. Although there are few studies of BD with opiate dependence, it has been described that the combination of opiate agonists and mood stabilizers often produces results which are difficult to obtain with the use of the two types of drugs separately (Maremmani et al. 2010).

When only the mood disorder responds to treatment, it is important to determine the effect the SUD may have on the recovery of the mood disorder. Some studies have demonstrated the ill effects on recovery from BD when the SUD goes untreated, while others have not found this to be the case (Pettinati et al. 2013). It is known that BD is less severe in patients who begin with alcohol abuse or dependence and then develop BD than in those who begin with BD (Winokur et al. 1995; Strakowski et al. 2005). The sequence of syndrome emergence and the age at onset of BD may offer some explanation. Age at onset of BD may be the most salient factor in understanding whether or not there will be a negative relationship between mood and substance use symptoms in patients treated for BD (Pettinati et al. 2013).

To summarize, different pharmacotherapies have been studied in open and non-blind studies and in small groups (Casas et al. 2008) and in the same well-controlled trials in which patients whose mood disorder had been stabilized were treated with a double-blind medication. In these studies, adding a medication to reduce substance use to a pharmacotherapy for treating bipolar disorder did not consistently reduce substance use in this patient group.

However, because of the low number of studies conducted and the small sample size of some of these, there is need for extensive controlled studies that include sufficiently large samples of patients of this complex condition.

118.2.4 Rapid Cycling

Rapid cycling is a very frequent situation among dual-bipolar patients, for this reason, some special recommendations should be taken into account (Casas et al. 2008):

- The obligations of adapting the rapid cycling treatment if the SUD presents itself as acute intoxication or abstinence syndrome.
- The best treatment of rapid cycling associated or not to acute intoxication or abstinence syndrome, regardless of the SUD-causing drug, is the atypical antipsychotics and/or antiseizure drugs.

- Regardless of the SUD causing rapid cycling, tricyclic antidepressants are inadequate treatments against a rapid cycling episode associated or not to an acute intoxication or abstinence syndrome.

118.2.5 Psychoeducational or Psychotherapeutics Approach

Psychotherapy with a psychoeducative approach is recommended to achieve better understanding of BD. As well, psychotherapy is considered adequate for the maintenance of abstinence, prevention of relapses, and improvement of drug treatment compliance (Casas et al. 2008). In BD group psychoeducation significantly reduced the number of relapsed patients and the number of recurrences per patient and increased the time to depressive, manic, hypomanic, and mixed recurrences. The number and length of hospitalizations per patient were also lower in patients who received psychoeducation (Colom et al. 2003). Even psychoeducation for caregivers of bipolar patients may improve long-term outcome in terms of time to recurrence. It has been showed the need to introduce psychological interventions early in the course of the illness as some treatments may be more useful in patients at earlier stages of BD (Reinares et al. 2010). In dual-bipolar patients, use/abuse of substances may worsen the BD. If the patient continues using drugs, above all, it should be attempted that he or she continues with the treatment. In this sense, the educative approach and reduction of harm from the SUD are very important (Casas et al. 2008).

Different forms of psychotherapy have been studied. Integrated Group Therapy to patients with BD and SUD has been found to be efficacious in reducing substance use. This was put forward after a pilot study was conducted in patients with this dual diagnosis, in which specific Integral Group Therapy was carried out with significant success in regard to the percentage of patients in abstinence versus those who had not followed an integrated therapy. Consequently, it seems to be a viable alternative to reduce substance abuse in patients with BD (Weiss et al. 2007). However, Integrated Group Therapy's length (20 sessions) and need for highly trained therapists may limit its adoption in substance use disorder community treatment programs. So a briefer (12-session) version of Integrated Group Therapy was compared, led by substance use disorder counselors without previous cognitive-behavioral training or BD experience, to group drug counseling. Analyses of primary outcomes showed trends favoring Integrated Group Therapy, with greater reduction in substance use during follow-up and diminished risk of mood episodes during treatment. Secondary analyses favored Integrated Group Therapy, with a significantly greater likelihood of achieving total abstinence, making it to the first abstinent month quickly and making for a "good clinical outcome" (a composite measure encompassing both substance use and mood simultaneously described by Weiss and cols.). Thus, a shortened version of Integrated Group Therapy can be delivered successfully by substance use disorder counselors, with better overall outcomes than those achieved with group drug counseling (Weiss et al. 2009).

118.3 Conclusion

It is known that BD and comorbid SUDs (dual diagnosis/disorders) are frequently found in the common psychiatric practice. Considering the comorbidity of BD associated to SUD and the few publications existing on it (with reduced sample sizes), efforts should be done to define some action guidelines in the management of this dual diagnosis. However, given the importance and incidence of this dual disorder, it is necessary to continue to study its nosological description in greater depth and also that of the action of its clinical-therapeutic approach (Casas et al. 2008).

This combination of entities is characterized by frequent relapses, suicide attempts, elevated impulsivity, poor adherence, and poor response to treatment. The substances that were most frequently used in BD were alcohol, nicotine, and cocaine. It is important to warm patients with BD about the risk of developing SUD and to stress the importance of early detection and treatment.

Some practical recommendations could be suggested: a visit every 2 weeks and hospital admission for patients with uncontrolled SUD and BD, as well as those with a risk of suicide and that Integral Group Therapy was carried out.

In regard to treatment with drug agents, there is a bibliography regarding the use of lithium and valproate in dual-bipolar patients, especially with alcohol abuse. Equally, a literature and series of studies, although with unequal results, are found in relationship to the use of carbamazepine, gabapentin, topiramate, lamotrigine, and atypical antipsychotics, among others. At least, six published double-blind placebo-controlled trials have targeted dual-bipolar adults, including valproate, quetiapine, acamprosate, naltrexone, and citicoline. However, antiseizure agents are profiled as the most promising treatments. In addition, there is an increase in the use of atypical antipsychotics, although there are few double-blind, controlled studies and the role of the adjuvant therapy for SUD must still be evaluated.

The existence of so many treatment alternatives may be due to the lack of conclusive studies in this disorder. Thus, it is recommendable to conduct prolonged controlled studies that include sufficiently large patient samples in this complex condition. However, it is unlikely that a single therapy will be developed in the near future due to the heterogeneity of patients with BD and SUD. Although it will be possible to identify the most appropriate therapies based on scientific evidence, until then the recommendations including heroin should be updated in future reviews.

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Comorbid Anxiety and Alcohol or Substance Use Disorders: An Overview

119

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Contents

Abstract

The comorbidity between anxiety and alcohol or substance use disorders represents a common and serious clinical challenge, characterized by a high worldwide prevalence. The co-occurrence of these disorders complicates treatment, management, and prognosis of both disorders, but it remains often unrecognized and untreated. Mental health professionals should accurately assess and evaluate the comorbidity, although related etiological links and temporal relationships are still unclear and, probably, heterogeneous and multifactorial. Alcohol and substances may be misused by individuals to self-medicate their anxiety, avoidant, and phobic symptoms, but also anxiety disorders may be consequences of alcohol and/or substance misuse. Integrated treatment appears the most promising approach, but there is paucity of evidence on pharmacological and

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non-pharmacological treatments addressed to both anxiety and substance use disorders. This chapter provides a comprehensive overview of main epidemiological and clinical issues, etiological/temporal links hypotheses, and treatment options for the comorbidity between anxiety and addictive behaviors.

119.1 Introduction

Comorbid anxiety and alcohol or substance use disorders represent a serious clinical challenge, influencing both treatment and prognosis (Smith and Randall 2012). Clinical evidence demonstrates that people with anxiety disorders, such as social phobia, generalized anxiety, panic, agoraphobia without history of panic, and specific phobia disorders, often misuse alcohol and prescription (e.g., benzodiazepines) and/or illicit drugs (e.g., stimulants or cannabinoids), developing substance abuse or dependence. At the same time, individuals primarily treated for an alcohol or drug use disorder are more likely to suffer from a comorbid anxiety disorder, due to the effect of substances in inducing anxiety symptoms (Pasche 2012).

All clinicians and mental health professionals who care for people with anxiety and substance use disorders should have a comprehensive knowledge of main relevant clinical and epidemiological issues such as:

- Prevalence and correlates of substance use disorders among subjects suffering from anxiety disorders
- Etiological hypotheses and temporal relationships underlying this comorbidity
- Methods to assess this comorbidity and to classify comorbid anxiety and alcohol/substance use disorders, taking mainly into account important changes introduced by the recently released fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association 2013)
- Specific clinical features, course, and prognosis of people suffering from this comorbidity
- Main evidence on preventive and treatment strategies

In this chapter, we aimed to present a comprehensive overview on these issues, highlighting data derived from research which may be useful to the clinical routine.

119.2 Epidemiological and Clinical Issues

119.2.1 Epidemiology

Comorbid anxiety and alcohol or substance use disorders are highly prevalent both in general and clinical populations (Pasche 2012). Data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) on 43,093 adults shows that the 12-month prevalence of any DSM-IV substance use disorder among respondents with a 12 month DSM-IV independent anxiety disorder is 15.0 % (Grant et al. 2004). As regards specific drug use disorders involved, cannabis use was the most common (15.1 %), followed by cocaine (5.4 %), amphetamine (4.8 %),

hallucinogen (3.7 %), opioid (3.2 %), sedative (2.6 %), tranquilizer (2.5 %), and inhalant/solvent (0.6 %) use disorders (Conway et al. 2006). People suffering from any anxiety disorder had an odds ratio (OR) of 1.9 (1.7–2.1) for any substance use disorder and of 1.7 (1.5–2.0) for any alcohol use disorder. The likelihood to develop a dependence syndrome was high with ORs of 2.8 (2.4–3.2) and 2.6 (2.2–3.0) for substance and alcohol dependence, respectively (Grant et al. 2004). Panic disorder with agoraphobia seems to show the strongest association with a co-occurring substance use disorder.

Other relevant data from North American samples are provided by the Mental Health Supplement to the Ontario Health Survey (Gratzer et al. 2004), a Canadian study on 7,195 individuals aged 15–64 years, and interviewed using the World Mental Health Composite International Diagnostic Interview (CIDI). A lifetime alcohol abuse or dependence by diagnostic subgroup was found in 8.7 % of people with any anxiety disorder (OR vs. healthy controls: 3.4; 95 % CI: 1.6–7.1) and in 18.0 % of people with comorbid anxiety and depressive disorders (OR vs. healthy controls: 7.6; 95 % CI: 3.5–16.7).

Relevant epidemiological data are available also from European populations. Data from the French representative sample of the Mental Health in General Population (MHGP) survey (Leray et al. 2011) on 36,105 adults showed a prevalence for alcohol abuse of 7.1 %, 6.5 %, 4.9 %, and 3.6 % among subjects suffering from agoraphobia, panic disorder, social phobia, generalized anxiety disorder, respectively. The results highlighted an OR of 1.7 (1.4–2.0) for alcohol abuse among people with any anxiety disorder. Similar results were found for drug addiction, with a prevalence of 6.5 %, 4.4 %, 3.7 %, and 2.8 % among individuals suffering from panic disorder, social phobia, agoraphobia, and panic disorder, respectively. Drug addiction was significantly associated with the diagnosis of any anxiety disorder, with an overall OR of 2.1 (1.8–2.5).

Baseline data from the Netherlands Study of Depression and Anxiety (NESDA), including 2,329 subjects with lifetime DSM-IV anxiety (social phobia, generalized anxiety disorder, panic disorder, agoraphobia) or depressive disorders and 652 controls, showed a significant association between alcohol dependence and comorbid anxiety disorder (OR: 2.4; 95 % CI: 1.5–3.8) or for an anxiety disorder associated to a depressive disorder (OR: 4.3; 95 % CI: 3.0–6.2) (Boschloo et al. 2011).

Epidemiological data are available also from the National Survey of Mental Health and Well-Being (NSMH&WB) conducted in Australia. This study, involving more than 10,000 adults, showed that the respondents with an alcohol use disorder (abuse or dependence) were three times more likely to suffer from a 12-month anxiety disorder. On the other hand, people suffering from any anxiety disorder had a prevalence of 16.0 % for any past-year alcohol use disorder (Burns and Teesson 2002).

Finally, some relevant epidemiological information is available also from Latin America. For example, a cross-sectional household survey in a sample of 2,302 Brazilian adults from Bahia, Brazil (Almeida-Filho et al. 2007), highlighted a prevalence of comorbid anxiety disorders and alcoholism of 14.4 %, with an OR of 2.7 (1.7–4.2).

Generally, the comorbidity between anxiety and alcohol or substance use disorders appears a worldwide phenomenon, with similar prevalence rates and high and significant risk of co-occurrence as compared with general population.

119.2.2 Etiological Hypotheses and Temporal Relationships

The underlying mechanisms influencing the association between anxiety and alcohol/substance use disorders are unclear because of relevant clinical heterogeneity as different drugs and alcohol may not share identical relationships with different anxiety disorders (Kushner et al. 2000). Three main etiological hypotheses are worth to be mentioned.

First, an anxiety disorder may be a direct predictor of addictive behaviors. This direction of the association is supported by evidence suggesting that some individuals may use alcohol and/or illicit substances to self-medicate their anxiety or depressive symptoms (the "self-medication" hypothesis) (Mueser et al. 1998). For example, alcohol shares many pharmacological effects with sedatives, anxiolytic agents, hypnotics, or anticonvulsants drugs (Lingford-Hughes et al. 2002). Further scientific support for the "self-medication" hypothesis comes from longitudinal studies. Data from the NESARC on 34,653 US adults showed that those who had used alcohol or other drugs for the purpose of reducing their fear, anxiety, or avoidance had a significant risk of incident alcohol or substance dependence, with adjusted ORs of 2.6 (1.0–6.7) and 5.0 (1.7–14.2), respectively (Robinson et al. 2011). However, further findings from NESARC (Martins and Gorelick 2011) did not support the self-medication hypothesis, highlighting that both mood and anxiety disorders may influence the transition from substance use to abuse and/or dependence rather than from abstinence to use. The representative National Comorbidity Survey (NCS) showed that a self-medication intent was present in 21.9 % of individuals with any anxiety disorder, with the highest prevalence (35.6 %) among people with a generalized anxiety disorder (Bolton et al. 2006). More generally, social phobia has been predominantly identified as a primary disorder preceding substance use, though the temporality of other anxiety and substance use disorders is less clear (Pasche 2012).

The second etiological hypothesis posits that alcohol and other substances directly promote the development of anxiety syndromes, in terms of consequences of chronic alcohol/substance use and/or related withdrawal syndromes (Kushner et al. 2000). For example, although alcohol is a fast-acting and effective anxiolytic agent, it can also increase the levels of anxiety, when the consumption is excessive and the subjects develop withdrawal symptoms, which determine a vicious cycle between anxiety and alcohol use (Lingford-Hughes et al. 2002). Another relevant example involves early cannabis exposure that may be related to the subsequent development of an anxiety disorder. A recent study (Degenhardt et al. 2013) on a cohort of 1,756 young Australians recruited in secondary schools showed that the continuity of cannabis use from adolescence to the age of 29 was associated to a risk 3–4 times higher of having a comorbid anxiety disorder. Data from the Netherlands

Mental Health Survey and Incidence Study (NEMESIS), a prospective study on 3,854 adults who had no lifetime anxiety disorders at baseline, highlighted a significant association between baseline cannabis use and 3-year incidence of any anxiety disorder (especially generalized anxiety and panic disorders), after adjusting for age, gender, education, urbanicity, employment, and partner status (van Laar et al. 2007).

Furthermore, the existence of anxiety disorders induced by specific classes of substances, such as alcohol, cannabis, cocaine/other stimulants, opioids, is supported by different neurobiological findings. Recent advances on the complex relationships between stress, anxiety, and alcohol use disorders show that synaptic communication in brain regions regulating stress and anxiety-related behaviors, such as amygdala and bed nucleus of the stria terminalis, is modulated by endogenous factors like dopamine and corticotropin-releasing factor (CRF) as well as by acute and chronic use of alcohol (Silberman et al. 2009). The CRF, a stress-related neuropeptide, has been implicated also in the anxiogenic effects of cocaine withdrawal, as well as in some of long-term effects of cocaine (Erb et al. 2006). Cannabis, mainly through the cannabinoid type 1 (CB1) receptors, can induce biphasic responses on anxiety- and fear-related behaviors. Generally, low doses of cannabis tend to induce anxiolytic-like effects, whereas high doses often cause an increase of anxiety symptoms (Moreira and Wotjak 2010). Finally, as regards heroine, morphine, or other opioids, it should be highlighted that the opioid system seems to play a key role in the neural modulation of anxiety. The activation of opioid system leads to anxiolytic effects both in healthy subjects and in individuals suffering from anxiety disorders since the opioid neurotransmission may serve as an adaptive mechanism addressed to blunt acute negative and distressing affective responses (Colasanti et al. 2011). At the same time, blockade or downregulation of opioid systems and second messengers is associated with the occurrence of severe anxiety, similar to opiate withdrawal (Colasanti et al. 2011).

Finally, there may be an independent mediator explaining the relationship between anxiety and alcohol/substance use disorders rather than a direct causal association. Generally, studies on the common-factor models for anxiety and substance use disorders are limited, and publications directly addressing this topic are sparse (Smith and Randall 2012) and focused on alcohol use disorders. Anxiety and alcohol or substance use disorders may share genetic and environmental factors, such as a disruptive family environment and parental abuse or neglect (Kushner et al. 2000). Especially among women, a childhood traumatic event might be at least partially responsible for the association between these two disorders (Marquenie et al. 2007). Mediators of the relationship between anxiety disorders and addictive behaviors may be also some personality traits characterized by a high level of anxiety sensitivity (Smith and Randall 2012). Individuals with increased levels of sensitivity to anxiety, and who do not have a diagnosable anxiety disorder, may be more likely to develop both anxiety and alcohol or substance use disorders. Furthermore, it has been investigated whether some molecular mechanisms could represent the common factor between anxiety and alcohol/substance use disorders. For example, it has been hypothesized that a decreased function of cAMP response

element-binding protein (CREB) in the central nucleus of the amygdala might regulate both anxiety and alcohol intake via the reduced expression of neuropeptide Y (NPY) and, therefore, might provide a common link between anxiety and alcohol use disorders (Pandey 2003).

119.2.3 Diagnosis and Classification

Anxiety disorders among people suffering from substance use disorders, as well as alcohol or drug addictive behaviors among people with an anxiety disorder, remain often unrecognized and, consequently, untreated. Despite scientific background of this comorbidity is mainly based on DSM-IV-TR criteria (American Psychiatric Association 2000), future diagnostic issues should necessarily take into account modifications approved by the recently released DSM-5 (American Psychiatric Association 2013). As regards anxiety disorders, these no longer include neither obsessive-compulsive disorder (now in the "obsessive-compulsive and related disorders" chapter) nor posttraumatic and acute stress disorders (included in the "trauma- and stressor-related disorders" chapter). At the same time, DSM-5 includes several changes in criteria of the new chapter "Substance-Related and Addictive Disorders," such as the exclusion of the abuse/dependence dichotomy, the introduction of craving as a diagnostic criterion, and the dimensional classification of alcohol and substance use disorders. However, no studies on vulnerable populations, such as those suffering from psychiatric disorders, are still available.

Actually, all subjects suffering from any anxiety disorders should be screened for alcohol or substance use disorders at the initial assessment. Early diagnosis and treatment can improve consistently course, prognosis, and treatment outcomes of both disorders. However, often it is difficult to ascertain the diagnosis and to assess whether anxiety symptoms are alcohol or substance induced or represent signs of an independent anxiety disorder (Smith and Randall 2012). Because of the overlapping of symptoms, a detailed interview is often a step needed to fully differentiate symptoms, which should resolve with abstinence, from anxiety and alcohol/substances use disorders. Therefore, it is important to carefully assess not only symptoms but also distinct diagnoses and clinical syndromes using structured diagnostic interviews, such as SCID (Structured Clinical Interview for DSM Disorders) (First et al. 2002), CIDI (Composite International Diagnostic Interview) (Robins et al. 1988), or MINI (Mini-International Neuropsychiatric Interview) (Sheehan et al. 1998). The Psychiatric Research Interview for Substance and Mental Disorders (PRISM) is a semistructured diagnostic interview, designed to maximize reliability and validity in alcohol, drug, and co-occurring disorders, individuals with a good reliability for many psychiatric diagnoses, including substance use and some anxiety disorders (Hasin et al. 1996).

Observing symptoms over a sustained period of abstinence may represent the best way to differentiate substance-induced from independent anxiety disorders. Anxiety may return to baseline levels after the period of withdrawal, so clinicians

should always reevaluate and reassess clinical features after 2–3 weeks of abstinence (Lingford-Hughes et al. 2002). The minimum duration of abstinence to establish the presence of an independent or substance-induced anxiety disorder is heterogeneous and based on half-life of involved drugs. For example, some benzodiazepines or methadone may require several weeks of abstinence to exclude a secondary anxiety disorder, whereas alcohol or cocaine necessitates shorter periods of abstinence to make valid diagnoses (Back and Brady 2008).

In order to diagnose a primary, and not substance-induced, psychiatric disorder, clinicians should verify whether (a) the onset of symptoms occurred before the substance use disorder, (b) the symptoms persist after a period of abstinence according to the characteristics of withdrawal course of each substance, and (c) symptoms exceed those produced by the specific misused substance. On the other hand, clinicians should suspect a secondary anxiety disorder if (a) the anxiety syndrome develops only during periods of active alcohol or substance misuse, (b) the symptoms are well-matched with specific symptoms of intoxication or withdrawal of the involved substance, and (c) the age at onset is atypical for a primary anxiety disorder.

A significant amount of alcohol and substance use screening tools are available and may be helpful to detect potential disorders. For example, the ASSIST (Alcohol, Smoking and Substance Involvement Screening Test), developed for the World Health Organization (WHO), is used to detect substance use and related problems in primary and general medical care settings (Humeniuk et al. 2008). As regards alcohol use disorders, AUDIT (Alcohol Use Disorders Identification Test) (Saunders et al. 1993) is probably the most widely used screening tool. Relatively recent data from the NESDA (Boschloo et al. 2010), including 1,756 individuals suffering from a past-year depressive and/or anxiety disorder, showed that AUDIT accurately detected alcohol dependence in depressed and/or anxious men and women, as compared to the gold standard of a CIDI-based diagnosis. However, the overall accuracy in detecting alcohol abuse was limited, without appropriate and identifiable cutoff scores for sensitivity and specificity.

The Addiction Severity Index (ASI) is a multidimensional and semistructured interview used to measure substance use severity, health-related outcomes, and social problems in individuals suffering from alcohol and other drug use disorders, both at admission to treatment and at follow-up (McLellan et al. 2006). The ASI can be used appropriately for screening of anxiety disorders, since the clusters of psychological composite scores are significantly related to a current psychiatric diagnosis, especially depressive and anxiety disorders (Dixon et al. 1996). Therefore, this instrument may be useful for both evaluation of the substance use severity and screening of patients who need an additional evaluation or treatment for their comorbid psychiatric disorder.

However, psychometric scales and diagnostic interviews need to be always integrated with all other information sources useful to assess and differentiate primary and secondary anxiety disorders. Laboratory data, age of onset of anxiety and substance disorders, collateral information, and a family history for anxiety and/or substance use disorder should be accurately collected.

119.2.4 Clinical Features, Course, and Prognosis

According to a recently published systematic review (Whiteford et al. 2013), anxiety, illicit drug, and alcohol use disorders accounted, respectively, for 14.6 %, 10.9 %, and 9.6 % of overall disability-adjusted life years (DALYs) caused by mental and substance use disorders.

The comorbidity between anxiety and substance use disorders makes difficult treatment and management of both disorders, with mutual negative effects. Individuals with an alcohol use and co-occurring anxiety disorders are significantly more disabled and use health services more than individuals without this comorbidity (Burns and Teesson 2002). Furthermore, subjects with comorbid generalized anxiety and substance use disorders are more likely than those with a generalized anxiety disorder only to have a lifetime history of any psychiatric disorder, pathological gambling, and an antisocial personality disorder (Alegría et al. 2010). A severe current alcohol dependence represents an important risk factor for unfavorable course of depressive and/or anxiety disorders, with persistent and unremitted symptoms (Boschloo et al. 2012a). The relationship is bidirectional, since the severity of depressive/anxiety symptoms is an additional independent predictor of the recurrence of an alcohol dependence (Boschloo et al. 2012b). A recent study (Magidson et al. 2012) compares substance users with and without a comorbid generalized anxiety disorder. The results showed that the co-occurring generalized anxiety disorder had a significant impact for what concerns a worse health-related quality of life, higher rates of treatment seeking, and greater self-reported drug use at follow up, supporting the need to define specific treatment options for this clinical population. Similar results were found from the National Comorbidity Survey (NCS) in a variety of clinical domains, such as rates of health-care utilization, additional psychiatric diagnoses, physical health problems, and interpersonal stress. Among most of comorbid individuals, social anxiety disorder onset predated that of alcohol dependence, with the former increasing the vulnerability for misusing alcohol (Buckner et al. 2008).

Anxiety disorders are well-known conditions associated to suicidal behaviors. Patients with anxiety disorders are 3.0–3.5 times more likely to complete suicide, 2.5–3.0 times to have suicidal ideations, and 2.5 times to attempt suicide (Kanwar et al. 2013). A comorbidity for an alcohol or a substance use disorder may consistently increase this risk. Findings from NESARC study (Nepon et al. 2010) highlighted that individuals with both substance use and any anxiety disorder had an OR of 3.2 (2.4–4.3) for suicide attempts as compared with people without these psychiatric conditions. Furthermore, substance users with co-occurring anxiety disorders showed a significant higher risk ($OR = 1.6$; 95 % CI: 1.3–2.0) of suicide attempts than those without this comorbidity.

All these findings support the need of further research on innovative intervention strategies to optimally treat co-occurring anxiety and substance use disorders and to prevent clinically severe consequences.

119.2.5 Treatment and Management

Although several pharmacological and psychological treatments such as cognitive-behavioral therapy have been studied for treatment of anxiety disorders, there is a paucity of evidence on effective treatments for the comorbidity with alcohol or substance use disorders. Furthermore, relevant management is complicated because of different patterns of anxiety and substance use disorders may interact, making difficult to generalize results (Watkins et al. 2005). New research directions for treatment of comorbid anxiety and substance use disorders are actually needed and should be focused on (a) identification of specific comorbid relationships between these disorders and their underlying processes (e.g., anxiety sensitivity), (b) mechanisms that may maintain the comorbidity, and (c) well-conducted evaluations of treatments that target these mechanisms (Baillie et al. 2010).

Treatment of co-occurring anxiety and alcohol or substance use disorders can be oriented either by dealing primarily with one of the two disorders (generally the more compelling in terms of severity) or, alternatively, by addressing these together. Over the past several decades, empirical studies and clinical guideline recommendations have undergone a broad shift in approaching this comorbidity, highlighting the importance to provide simultaneous and integrated treatment for both disorders, regardless of the status of the comorbid condition (Watkins et al. 2005). However, research conducted in this field has yielded inconsistent results, with some studies demonstrating no clear advantage for the simultaneous treatment of anxiety disorders and addictive behaviors (Pasche 2012). For example, a relatively recent meta-analysis (Hobbs et al. 2011) suggests that, due to the potential serious consequences of unsuccessful treatment for alcohol use disorders, an integration with interventions addressing co-occurring anxiety disorders could be important, even if the amount of absolute benefit is moderate or even smaller. Inconclusive results were shown also by a systematic review (Hesse 2009) analyzing integrated psychosocial treatment for substance use and comorbid anxiety or depressive disorders, as, though promising, these did not give any significant additional benefit. Generally, a potentially effective strategy may be the early treatment of the disorder the patient is ready to address, while, simultaneously, a motivational approach may be used to improve readiness to change the comorbid problem (Smith and Book 2008).

At the same time, there is a lack of consistent evidence for effective pharmacological interventions for both anxiety and substance use disorders, whereas only sporadic intervention studies are available from the scientific literature, e.g., for alcohol use disorders. Selective serotonin reuptake inhibitors (SSRIs) seem effective in reducing and preventing anxiety symptoms, but there is a lack of clinical trials assessing their efficacy in comorbid patients. In a small placebo-controlled trial (Randall et al. 2001) on 15 outpatients with an alcohol dependence and social phobia, the paroxetine-treated group showed significantly lower symptoms on Clinical Global Index (CGI) and the Liebowitz Social Anxiety Scale, as compared with the placebo group, but there was a nonsignificant effect on quantity/frequency

measures of drinking. Studies on Buspirone, a partial 5-hydroxytryptamine 1A agonist, have shown mixed results on comorbid generalized anxiety and alcohol use disorders (Back and Brady 2008). Although benzodiazepines are effective in the treatment of anxiety disorders, their use in individuals with current or lifetime alcohol or substance use disorders may be complicated by their potential for abuse and dependence. More generally, although the use of medications for comorbid psychiatric disorder is encouraged, evidence is inconclusive whether there is the need of full detoxification before starting psychopharmacological treatment (Watkins et al. 2005).

Finally, use of agents specifically addressed to substance use disorders in individuals suffering from comorbid anxiety disorders is underexplored (Back and Brady 2008). In one randomized study conducted at three Veterans Administration outpatient clinics on 254 patients with an axis I psychiatric disorder and alcohol dependence, the efficacy of disulfiram and naltrexone, or their combination, was investigated. Subjects treated with an active medication showed more consecutive weeks of abstinence and less symptoms of craving than those treated with placebo, but there were no significant differences in other measures of alcohol consumption. Furthermore, subjects treated with disulfiram experienced significantly fewer obsessive-compulsive and phobic symptoms over time, whereas no clear advantage of combining medications was observed (Petrakis et al. 2005).

A secondary analysis of a study evaluating efficacy of naltrexone 50 mg⁄day in veterans suffering from alcohol dependence showed that among subjects taking antidepressant medications for mood and anxiety symptoms, those randomized to naltrexone had significantly smaller percent drinking days than those receiving placebo. On the other hand, for patients not on antidepressant medication, the difference between naltrexone and placebo groups was not significant (Krystal et al. 2008).

119.3 Conclusion

The dual diagnosis between anxiety and co-occurring alcohol or substance use disorders is a common but serious clinical problem. This comorbidity tends to complicate treatment, management, and prognosis of both disorders. Clinicians face a number of heterogeneous combinations of anxiety and substance use disorders. The prevalence of alcohol or substance use disorders among subjects with anxiety disorders is high worldwide. Etiological links and temporal relationships of this comorbidity are still unclear and, probably, multifactorial. Alcohol and substance may be misused by individuals in order to self-medicate their anxiety, avoidant, and phobic symptoms, though this remains often unrecognized and untreated. Clinicians should assess this comorbidity using structured diagnostic interviews and observing symptoms over a sustained period of abstinence to differentiate substance-induced from independent anxiety disorders. A comprehensive diagnostic assessment should include also several alcohol and substance use screening tools, such as ASI, ASSIST, and AUDIT questionnaires. While some pharmacological and psychosocial treatments

have shown effectiveness for separate treatment of anxiety and substance use disorders, there is a lack of evidence on treatments addressed to both disorders as dual diagnosis label means more complex needs rather than two distinct problems (Carrà and Clerici 2006).

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The Comorbidity of Post-Traumatic-Stress Disorder (PTSD) and Substance Use Disorders

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Abstract

Posttraumatic stress disorder (PTSD) and substance use disorders (SUDs) frequently co-occur. Among individuals seeking treatment for SUDs, approximately 30 % to 50 % meet criteria for lifetime PTSD. Epidemiologic surveys demonstrate that individuals with PTSD have 4-5 times more likely to have a SUD at some point in their lives compared to individuals who do not have PTSD. Self-medication and susceptibility are two hypotheses that have been proposed to help explain the etiological relationship between PTSD and SUDs. It is also possible that common factors, such as genetic, neurobiological, or environmental factors, contribute to the high rate of PTSD-SUD co-occurrence. Integrated psychotherapy approaches for the treatment of patients with both disorders show promise. There are also a number of pharmacotherapeutic agents that have demonstrated preliminary efficacy in the treatment of co-occurring PTSD/SUD, but further investigation is needed. This chapter reviews these and other advances in the study of comorbid PTSD and SUDs, and suggests areas for future work.

120.1 Introduction

Posttraumatic stress disorder (PTSD) is a psychiatric disorder that occurs after exposure to an event (experienced or witnessed) involving actual or threatened death, serious injury, or threat to the physical integrity of oneself or others. The traumatic event must be followed by at least 1 month of symptoms, such as intrusive recollection, avoidance or emotional numbing, and hyperarousal, that interfere with the individual's ability to function. Substance use disorders (SUDs) commonly co-occur with PTSD. Moreover, comorbid PTSD/SUD is associated with a more complex and costly clinical course when compared with either disorder alone, so identification and treatment of both illnesses in individuals with comorbidity is essential to optimize clinical care.

Discussions of international issues in co-occurring PTSD and substance use are complicated by a number of factors. Definitions and experiences of trauma are culturally bound and in many countries can be connected with issues of politics and social justice. There is also debate about the cross-cultural application of the DSM-defined PTSD criteria. Modifications of the DSM criteria and textual modification have been suggested to improve cross-cultural applicability (Hinton and Lewis-Fernandez 2011). Similarly, patterns of substance use and definitions of SUDs also occur in cultural contexts that can tremendously alter the perspectives of acceptable use and willingness to honestly report use. In addition, we do not have accurate estimates of prevalence of either SUDs or PTSD alone or the comorbidity in many areas of the world. So, in the sections that follow, much of the data that is presented is based on studies conducted in a few countries. However, the diagnostic, phenomenologic, and neurobiologic underpinnings of the relationships and treatment options for PTSD and SUDs discussed are likely to apply broadly.

120.2 Epidemiology of PTSD/SUD Comorbidity

120.2.1 United States

Prevalence estimates for PTSD, SUD, and comorbid PTSD/SUD among US adults are primarily garnered from three sources: national epidemiological surveys and Veteran and treatment-seeking populations. Early estimates were provided by the National Comorbidity Survey (NCS; $N = 8{,}098$), conducted from 1990 to 1992, indicated a 7.8 % lifetime prevalence for PTSD and a 26.6 % lifetime prevalence for SUD among the general population (aged 15–54), (Kessler et al. 1994, 1995). Individuals with PTSD were between two and four times more likely to meet criteria for an SUD than those without PTSD. A decade later, the National Comorbidity Survey – Replication (NCS-R; $N = 5{,}692$) indicated a 6.8 % lifetime prevalence of PTSD and 35.3 % lifetime prevalence of any SUD (Kessler et al. 2005; Harvard School of Medicine 2007). More recently, the 2010 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC; $N = 34{,}653$) estimated that 6.4 % of the population met lifetime criteria for PTSD, more than one in five (22.3 %) of those with PTSD met criteria for drug abuse or dependence, and nearly half (46.4 %) met criteria for any SUD (Pietrzak et al. 2011).

Veterans constitute a population of particular interest due to their increased risk for developing both PTSD and SUDs in comparison to the general population (Kang et al. 2003; Hoge et al. 2004; Sabella 2012). Post-deployment prevalence rates have been estimated at approximately 21 % for SUDs and between 15 % and 20 % for PTSD among Veterans of Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) (Hoge et al. 2004; Bray and Hourani 2007; Seal et al. 2007; Thomas et al. 2010). Severity of combat exposure has been directly linked to risk for development and chronicity of PTSD symptoms (Kang et al. 2003) and misuse of substances (Santiago et al. 2010). Administrative data from the Department of Veterans Affairs indicate that among Veterans serving in the Vietnam era or later, almost half (41.4 %) with an SUD were also diagnosed with PTSD (Petrakis et al. 2011). Conversely, a recent study followed a large cohort of Veterans diagnosed with PTSD ($n = 272{,}509$) over a 3-year timeframe and found that nearly one in five (19.33 %) were diagnosed with a comorbid SUD and presence of a comorbid SUD was positively associated with mortality at follow-up (hazards ratio = 1.70; Bohnert et al. 2013).

Treatment-seeking individuals have rates of comorbid PTSD and SUD that are consistently higher than the general population. Patients seeking treatment for PTSD are up to 14 times more likely than patients without PTSD to have an SUD (Jacobsen et al. 2001; Chilcoat and Menard 2003; Ford et al. 2007). Conversely, among patients seeking treatment for SUDs, lifetime PTSD rates range from approximately 30 % to over 60 % (Dansky et al. 1994; Triffleman et al. 1995; Back et al. 2000; Clark et al. 2001; Brady et al. 2004). Finally, a multimodal assessment of comorbidity among patients at a level I trauma surgery center indicated that 79 % had one or more SUD and/or PTSD comorbidity; three in

four (74 %) met criteria for an SUD, whereas one in four patients endorsed symptoms consistent with PTSD (Zatzick et al. 2012). Variations in prevalence estimates among treatment-seeking populations are most likely attributable to methodological differences, including differences in patient populations sampled and measurement techniques.

120.2.2 International Prevalence Estimates

As mentioned above, we do not have accurate prevalence estimates of the rates of either PTSD or SUDs in much of the world. While the World Health Organization (WHO) has sponsored a series of international studies of mental health disorders, the complexity of the trauma questions used, cultural differences in the definition of trauma, and reluctance to discuss traumatic events likely led to underestimates of PTSD prevalence (Kessler and Greenberg 2002). In general, the estimates for lifetime PTSD prevalence range from a low of 0.3 % in China to 6.1 % in New Zealand (Demyttenaere et al. 2004). As might be expected, some evidence suggests that the risk of PTSD is higher among people from less developed countries who have been exposed to prolonged traumatic experiences associated with wars and political and ethnic violence. For example, 65 % of Bosnian refugees resettled in the United States have PTSD (Weine et al. 1995) and 73 % of Palestinian children exposed to war trauma experienced PTSD (Thabet and Vostanis 1999). In a recent WHO survey, disability from common mental and physical disorders was assessed in nationally representative samples from 26 countries (Bruffaerts et al. 2012). While physical disorders were considerably more common than mental disorders, there was more disability associated with mental disorders as compared to physical disorders at an individual level. Of all physical and mental disorders, PTSD was associated with the highest level of disability.

While little is known about the prevalence of PTSD in many countries, even less is known about the prevalence of co-occurring PTSD and SUDs. An epidemiologic survey conducted in Australia in 2007 found that the 12-month prevalence of PTSD was 6.4 %, higher than the prevalence of any other anxiety disorder (National Survey of Mental Health and Wellbeing 2007). SUDs were much more common in individuals with mental illness as compared to those without mental illness, and nearly 40 % of those with anxiety disorders reported daily drug misuse. Data for PTSD specifically was not presented. This suggests that the common co-occurrence of PTSD and SUDs which has been found in the United States may exist in other countries. However, in an investigation of the prevalence of psychiatric disorders in South Africa (Stein et al. 2008), the authors note that local factors such as poverty and lack of access to substances may change the occurrence of certain psychiatric disorders and comorbidities.

120.3 Etiologic Relationship Between PTSD and SUD

120.3.1 Self-Medication Hypothesis

A number of theories have been posited to explain the etiology and functional associations between PTSD and co-occurring SUDs. The most prominent theory is the *self-medication hypothesis* (Khantzian 1985, 1990, 1997; Reed et al. 2007; Menary et al. 2011). According to the self-medication theory, substance use is negatively reinforced when it alleviates PTSD symptoms, such as sleep impairment, intrusive memories, nightmares, hyperarousal, and feelings of estrangement. In support of this theory, Saladin and colleagues (1995) compared individuals with PTSD only vs. PTSD/SUD and found that hyperarousal and avoidance symptoms were more severe among the comorbid PTSD/SUD group. Laboratory-based findings also provide support for the self-medication model. One study examined responsivity to trauma cues (i.e., presentation of personalized trauma narrative) and found that individuals with comorbid PTSD/SUD demonstrate increased craving for substances in response to the trauma cues (Coffey et al. 2002). Moreover, research has shown that trauma cue-elicited craving is significantly reduced following exposure therapy for PTSD (Coffey et al. 2006). Finally, increases in craving have been shown to be positively correlated with severity of PTSD symptoms (Saladin et al. 2003).

Among patients with PTSD/SUDs, the drug of choice (e.g., central nervous system depressant or stimulant) may reflect an attempt to alleviate a particular cluster of symptoms. For example, Saladin et al. (1995) found that PTSD/SUD individuals with more severe hyperarousal symptoms (Criterion D) were more likely to be dependent on alcohol than cocaine. Likewise, PTSD/SUD individuals with more severe avoidance (Criterion C) and flashback symptoms (Criterion B) were more likely to be dependent on cocaine. More recently, Tull and colleagues (2010) observed a significant relationship among PTSD hyperarousal symptoms and dependence on heroin, as opposed to crack/cocaine and alcohol dependence. In addition to self-medication of PTSD symptoms, individuals with PTSD/SUDs may also use substances to self-medication withdrawal symptoms, which may mimic symptoms of PTSD. For example, withdrawal from alcohol or drugs may result in sleep disturbances, difficulty concentrating, irritability and anger, and feeling "on edge." Thus, withdrawal symptoms may contribute to a reinforcing cycle of self-medication among individuals with PTSD/SUD.

Research examining the temporal order of onset of development of PTSD and SUDs also provides some insight with regard to etiology (Najt et al. 2011). In the majority of cases, the development of PTSD precedes the development of the SUD (Chilcoat and Breslau 1998; Compton et al. 2000; Jacobsen et al. 2001; Stewart and Conrod 2003; Back et al. 2005, 2006). Furthermore, PTSD and SUD symptoms have been shown to covary over time. For example, Ouimette and colleagues (2010) tracked weekly fluctuations in PTSD and SUD symptoms among 35 PTSD/SUD outpatients over a 26-week period. The findings provided support

for the self-medication hypothesis and showed that increases in PTSD symptoms were associated with increases in SUD severity. More recently, Simpson and colleagues (2012) used daily interactive voice response (IVR) to examine the relationship between PTSD symptoms and same-day as well as next-day alcohol craving among 29 outpatients entering SUD treatment (26/29 had PTSD). The findings showed that greater PTSD severity was associated with greater alcohol craving and greater hyperarousal symptoms were particularly associated with craving. Next-day craving was predicted by nightmares the previous night, emotional numbing, and hypervigilance. Finally, several studies investigating civilian and Veteran patients' perceptions of the interrelationship of PTSD and SUD symptoms demonstrate support for the self-medication hypothesis (Brown et al. 1998; Back et al. 2006).

The *high-risk hypothesis* (Chilcoat and Breslau 1998; Acierno et al. 1999) posits that the lifestyle of an individual with an SUD increases the likelihood of being exposed to a traumatic event and subsequently developing PTSD. For example, individuals with SUDs often spend time in dangerous environments and engage in high-risk behaviors associated with obtaining or using substances (e.g., prostitution, theft) that may put them at risk for experiencing a Criterion A event. The *susceptibility hypothesis* posits a biological vulnerability to developing PTSD among individuals with SUDs. Individuals who engage in chronic substance use often experience anxiety and arousal and exhibit poor coping skills (e.g., more avoidant or emotion-focused coping vs. problem-focused coping) (Sharkansky et al. 1999; Stewart et al. 2000; Jacobsen et al. 2001; Staiger et al. 2009). Lastly, there is some evidence that other common factors, such as genetics, common neurophysiologic systems, described below, and prior exposure to traumatic events, may play a role in the etiology of comorbid PTSD/SUD (Stewart and Conrod 2008; Kingston and Raghavan 2009; Khoury et al. 2010; Norman et al. 2012).

120.3.2 Neurobiology

A growing body of evidence from basic science and translational studies implicates common neurobiologic pathways and abnormalities involved in anxiety disorders and SUDs. One of the bridging neurobiologic constructs between anxiety disorders and SUDs involves the role of stress. Corticotrophin-releasing factor (CRF), one of the key hormones involved in the stress response, has been implicated in the pathophysiology of anxiety, affective, and addictive disorders. Stress stimuli that activate CRF circuits are also known to potentiate mesolimbic dopaminergic reward pathways in laboratory animals. Similarly, human laboratory studies have shown that emotional stress and negative affect states increase drug craving in drug- and alcohol-dependent individuals. Animal models indicate that early-life stress and chronic stress result in long-term changes in stress responses which can alter the sensitivity of the dopamine system to stress and increase susceptibility to self-administration of substances of abuse. This may provide the neurobiologic underpinnings of the well-established relationship between early-life adversity, PTSD, and SUDs in adolescents and adults (Brady and Sinha 2005).

120.4 Assessment

Symptom assessment is critical to the effective treatment of PTSD/SUD and should ideally encompass detection of trauma exposure and substance misuse, evaluation of diagnostic criteria for PTSD and SUD, and monitoring of symptom severity (Steenkamp et al. 2011; Tucker et al. 2011). Historically, instruments assessing PTSD and SUD were predominantly developed for use with in English-speaking, westernized cultures. However, in 1990, recognizing the need for cross-cultural assessment of mental illness, the World Health Organization (WHO) developed a tool that addressed criteria for both the American Psychiatric Association's Diagnostic and Statistical Manual and the International Classification of Disease (ICD). The resulting Composite International Diagnostic Interview (CIDI; Robins et al. 1989) was a comprehensive, structured, modular interview designed to assess mental disorders – including but not limited to PTSD and SUD. As of 2011, versions of the CIDI have been translated into approximately 25 languages for use in at least 20 countries (WHO 2004). Recognition of the important roles that culture and language play in the conceptualization, experience, and expression of PTSD and SUD is increasing (Westermeyer 1995; Hollifield et al. 2002). As a result, increased efforts have been made to translate and adapt a range of instruments previously validated with English-speaking populations (e.g., Mollica et al. 1992; Westermeyer 1995; Ertl et al. 2010; Ali et al. 2012) as well as to develop culturally specific instruments, to screen, diagnose, and monitor symptoms of PTSD and SUD in a variety of international populations (e.g., Dao et al. 2012; Jayawickreme et al. 2012; Kok et al. 2013).

Regardless of cultural context, there are several general constructs relevant to the assessment of PTSD and SUD. These constructs include determination of the presence, order of onset, frequency, duration, and severity of symptoms, as well as the degree to which symptoms interfere with or impair daily functioning, employment, and interpersonal relationships (for review, see Rodriguez et al. 2012). Several reviews of PTSD assessment (e.g., Hollifield et al. 2002; Elhai et al. 2005; Rodriguez et al. 2012; Wisco et al. 2012), SUD assessment (Westermeyer 1995; Fitch et al. 2004), and PTSD/SUD assessment (e.g., Jacobsen et al. 2001; Jane-Llopis and Matytsina 2006; Najt et al. 2011) are available in the extant literature. When assessing comorbidity, special consideration should be given to the relationships between symptoms, including PTSD symptoms as potential motivators for substance misuse. Validated self-report, semi-structured, and fully structured interview instruments are available to assist with (1) screening for trauma exposure, (2) screening for PTSD/SUD symptoms, (3) determining diagnosis, and (4) monitoring symptom change over time. Table 120.1 presents a sampling of validated measures frequently used in the assessment of PTSD and SUD.

In addition to self-report and interview, biological testing is recommended in assessing SUD and may overcome some of the culture-bound limitations of self-report and clinician-administered assessments. Urine drug screening (UDS) is the most common and preferred method for detecting illicit drug use given that it is cost effective and minimally invasive and provides a quantitative means for measuring the use of substance (Preston et al. 1997; Wolff et al. 1999; Richter and Johnson 2001).

Table 120.1 Assessment and screening instruments

Screening		
Measure	Source reference	Language/country of origin
Trauma life events questionnaire	Kubany et al. 2000	English
Short posttraumatic stress disorder rating interview (SPRINT)	Connor and Davidson 2001	English
PTSD checklist – civilian version, short form	Lang and Stein 2005	English
Trauma Screening Questionnaire (TSQ)	Brewin et al. 2002	English
Primary Care PTSD Screen (PC-PTSD)	Prins et al. 2003	English
Alcohol Use Disorders Identification Test (AUDIT)	Saunders et al. 1993	English
Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST)	Humeniuk et al. 2008	English
CAGE	Cooney et al. 1995	English
Drug Abuse Screening Test (DAST)	Gavin et al. 1989	English
Davidson Trauma Scale (DTS)	Ali et al. 2012; Davidson et al. 1997	English, Urdu/Uganda
HADStress	Gulden et al. 2010	Ethiopia
Diagnosis		
Clinician-Administered PTSD Scale (CAPS)	Blake et al. 1995	English
Alcohol use disorders and associated disabilities interview schedule	Grant and Hasin 1990	English
Anxiety Disorder Interview Schedule for DSM-IV (ADIS)	DiNardo et al. 1994	English
Composite International Diagnostic Interview, version 3.0	Robins et al. 1989	English, German, French, Dutch, Chinese, others
Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)	First et al. 1996	English
Mini-International Neuropsychiatric Interview (MINI)	Sheehan et al. 1998	English
Self-Report Inventory for PTSD (SRIP)	Kok et al. 2013	Dutch
Posttraumatic stress disorder interview for Vietnamese refugees	Dao et al. 2012	Vietnamese
Symptom monitoring		
Impact of events scale	Weiss and Marmar 1996	English
PTSD Checklist (PCL)	Blanchard et al. 1996	English
PTSD Symptom Scale (PDS)	Foa et al. 1993; Ertl et al. 2010	English; Bantu
Addiction Severity Index (ASI)	McLellan et al. 1992	English
Timeline Follow-Back (TLFB)	Sobell and Sobell 1995	Universal

(*continued*)

Table 120.1 (continued)

Screening		
Measure	Source reference	Language/country of origin
Symptom interaction		
Inventory of drinking situations	Annis et al. 1997	English
Drinking motives questionnaire	Cooper 1994	English
Inventory of drug-taking situations	Annis and Martin 1985	

Additional biological assessment options exist for use as either adjunctive or alternative assessments of SUD: testing of bodily fluids, such as blood and saliva, breathalyzer analysis for recent alcohol use, hair analysis techniques, and a blood-based testing method known as percent carbohydrate-deficient transferrin (Aithal et al. 1998; Wolff et al. 1999; Arndt 2001). These methods are less frequently used due to higher cost, increased invasiveness, false positives, and/or narrow detection windows (Widdop and Caldwell 1991; Jaffe 1998).

120.4.1 Psychotherapeutic Treatment

Historically, psychosocial treatment approaches for individuals with PTSD and SUDs have adhered to the *sequential treatment model*, in which the SUD is treated first and trauma work is deferred until a period of sustained abstinence (e.g., 3–6 months) has been achieved (Schnitt and Nocks 1984; Nace 1988). This generally entails two separate providers (i.e., one provider addresses SUD and another addresses PTSD) in two separate clinics with little cross-communication. Proponents of the sequential model state that (a) continued substance use will impede therapeutic efforts and/or (b) trauma-focused work may increase risk for relapse (Nace 1988; Pitman et al. 1991). However, there is little empirical data to support these concerns. Given the high co-occurrence of PTSD and SUDs, the covarying interrelationship between PTSD symptoms and substance use severity, as well patients' preferences for treatment (e.g., less than 30 % of patients prefer sequential treatments; Back et al. 2006), recent advances in psychosocial treatments have focused on the development and testing of *integrated treatment models*. In contrast to sequential treatments, integrated treatments are provided by the same clinician and address both the SUD and PTSD concurrently. The integrated model posits that addressing the PTSD symptoms early in treatment will likely improve recovery from SUDs, particularly if substances are being used to self-medicate trauma-related symptoms (Brady et al. 2001; Back 2010; Hien et al. 2010; Mills et al. 2012).

Compelling support for the integrated model is provided by recent investigations examining the temporal course of symptom improvement among PTSD/SUD patients. Among 94 outpatients with alcohol dependence and PTSD, improvements in PTSD symptoms had an impact on improvements in alcohol-dependence symptoms, but decreases in drinking did not impact PTSD symptoms (Back et al. 2006).

Hein and colleagues (2010) replicated these findings using data from a larger sample ($N = 353$) from a National Institute on Drug Abuse (NIDA) Clinical Trials Network (CTN) study. For every unit of PTSD improvement, the odds of being a heavy substance user at follow-up decreased more than fourfold (Hien et al. 2010). A growing body of literature examining the tolerability and efficacy of addressing PTSD among SUD patients demonstrates that substance use typically decreases significantly and does not increase with the addition of trauma-focused interventions (Triffleman 2000; Brady et al. 2001; Najavits et al. 2005; McGovern et al. 2009; Hien et al. 2010; Back et al. 2012; Mills et al. 2012).

Prolonged exposure (PE; Foa et al. 2007) therapy has been deemed one of the most effective treatments available for PTSD (IOM 2008), but there is limited research exploring its efficacy in substance-abusing populations. PE involves having the patient revisit the traumatic memories (i.e., imaginal exposures) and approach safe but anxiety-producing situations in real life that are avoided by the patient (e.g., in vivo exposures). A recent meta-analysis demonstrated large effect sizes for PE in comparison to control conditions (Powers et al. 2010). Furthermore, a longitudinal study conducted among 65 patients 5–10 years after receiving PE demonstrated maintenance of effects with only 17.5 % of patients meeting diagnostic criteria for PTSD (Resick et al. 2012). PE has demonstrated effectiveness in addressing PTSD among a variety of traumatic stress populations, including victims of rape, physical assault, refugees, motor vehicle accidents, combat, terrorism, childhood abuse, and mixed trauma types (Foa et al. 2005; McDonagh et al. 2005; van Minnen and Foa 2006; Bryant et al. 2008; Nacasch et al. 2011; Resick et al. 2012). Despite that fact that PE is one of the most effective treatments for PTSD, the majority of integrated treatment interventions developed to date generally do not include PE components. Rather, treatment tends to focus on psychoeducation, exploring the relationship between PTSD symptoms and substance use, self-management of symptoms and negative emotions, and development of cognitive behavioral coping skills (Miller and Guidry 2001; Ford and Russo 2006; McGovern et al. 2009).

One of the most widely used and investigated integrated treatments to date is *Seeking Safety* (SS), a non-exposure-based 24-session manualized therapy that prioritizes establishing and maintaining safety (Najavits et al. 1998; Hien et al. 2004, 2008). Other key concepts include anticipating dangerous situations, setting boundaries, anger management, and affect regulation. In a study of 107 women comparing SS to relapse prevention (Hien et al. 2004), both treatments resulted in improved substance use and PTSD severity; however, no significant between-group differences in PTSD or SUD symptoms were observed. In a larger national multisite community study, SS was compared to a women's health education (WHE) group (Hien et al. 2009) in 353 women. Both SS and WHE resulted in significantly improved PTSD symptoms; however, neither group resulted in a significant reduction in abstinence rates over time.

More recently, Back and colleagues developed an exposure-based, manualized cognitive behavioral therapy for PTSD/SUDs (Back et al. 2001, 2012) (in press). The treatment, *COPE* (*Co*ncurrent Treatment of PTSD and

Substance Use Disorders Using *P*rolonged *E*xposure), combines evidence-based cognitive behavioral therapy for SUDs (Carroll 1998) with the key components of prolonged exposure for PTSD (Foa et al. 2007), which includes both in vivo and imaginal exposure techniques. COPE was initially trialed as a 16-session, individual intervention and tested in an uncontrolled psychotherapy development study among patients ($N = 39$) presenting with comorbid PTSD and cocaine dependence (Brady et al. 2001). In this study, no signs of increased substance were observed with the inclusion of PE. Treatment completers demonstrated significant improvements in all PTSD symptom clusters and a significant reduction in cocaine use from baseline to end of treatment (Brady et al. 2001). Reductions in PTSD and SUD symptoms were maintained at 6-month follow-up. Mills and colleagues (2012) recently completed a randomized control trial of COPE plus treatment as usual (TAU) vs. TAU alone. Participants were 103 patients (62.1 % female) with civilian PTSD and SUDs in Sydney, Australia. For this trial, COPE consisted of 13, individual sessions. From baseline to 9-month follow-up, significant reductions in PTSD symptom severity were found for both groups; however, the COPE group demonstrated a significantly greater reduction in PTSD symptom severity (mean difference –16.09) and lower rates of PTSD diagnosis as compared to the control group (56.4 % vs. 79.2 %). No significant between-group differences in rates of abstinence, number of SUD dependence criteria met, or retention were found. The findings suggest that integrated PTSD/SUD treatments employing PE techniques for PTSD can be used safely without an increase in substance use, can lead to sustained improvements across various domains (e.g., depression), and produce greater improvements in PTSD than TAU. Currently, COPE is being evaluated as a 12-session intervention in a randomized controlled trial among Veterans, and the preliminary findings are positive (Back et al. 2012). Recently, prolonged exposure has been incorporated into existing residential SUD treatment with promising preliminary results supporting its safety, feasibility, and efficacy (Henslee and Coffey 2010; Berenz et al. 2012).

120.4.2 Pharmacological Treatment

There are relatively few studies of medication treatments for co-occurring PTSD and SUDs. Sertraline, a serotonin reuptake inhibitor with FDA approval for the treatment of PTSD, was investigated in a double-blind, placebo-controlled, 12-week trial (Brady et al. 2005). Individuals with early onset PTSD and less severe alcohol dependence demonstrated improvements in alcohol use severity with sertraline treatment, while individuals with later onset PTSD and more severe alcohol dependence evidenced more favorable alcohol use outcomes when treated with placebo. Petrakis and colleagues (2005) investigated the use of agents targeting alcohol consumption, disulfiram and naltrexone, alone or in combination, in outpatients with alcohol dependence (AD) and a variety of comorbid psychiatric disorders (42.9 % PTSD). Individuals treated with either drug evidenced fewer drinking days

as compared to those on placebo, and those treated with disulfiram reported less craving. Individuals receiving active medication demonstrated greater symptom improvement (e.g., less anxiety) pre- to posttreatment as measured by the Brief Symptom Inventory. No advantage of combining disulfiram and naltrexone was reported. In a more recent study (Petrakis et al. 2011), paroxetine (serotonin reuptake inhibitor) was compared to desipramine (norepinephrine uptake inhibitor) in men with both AD and PTSD. Desipramine was superior to paroxetine with respect to study retention and alcohol use outcomes. Although the serotonin uptake inhibitors are the only FDA-approved medications for the treatment of PTSD, the current study suggests that norepinephrine uptake inhibitors may present clinical advantages. Further investigation of the use of medications as an adjunct to psychotherapeutic treatment in the treatment of co-occurring PTSD and SUDs is needed.

120.5 Conclusion

In summary, while we do not have information about the international prevalence estimates of co-occurring PTSD and SUDs, many studies suggest that these two disorders commonly co-occur. A number of theories have been posited to explain the functional relationship between these disorders, and there are clear neurobiologic connections. Medication treatments have shown some promise, but more investigation is needed. In terms of psychotherapeutic approaches, integrated treatment has been accepted as a safe and effective model of treatment. Although non-trauma-focused treatments offer some PTSD symptom reduction, data suggests that trauma-focused, exposure-based treatment offers greater symptom reduction than non-exposure-based treatment in SU treatment programs. Recent evidence demonstrates that improvement in PTSD positively impacts substance use outcomes, clearly supporting a more rigorous approach to the assessment and treatment of PTSD among patients with SUDs.

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A Drug Treatment Program for Young Israeli-Military Veterans

121

Hagit Bonny-Noach and Haim Mell

Contents

Abstract

Over the last two decades, the phenomenon of drug use among Israeli military veteran backpackers in Southeast Asia and South America has become an Israeli problem requiring a social solution. The severe consequences of drug use among the young backpackers can be classified into two types: The first is related to the health consequences. These include mental problems following the use of various drugs. Some of them return from their backpacking trips in a psychotic state in various degrees of severity or other psychiatric conditions like depression or anxiety. The second is related to the law: breaking of local laws, police arrests, and incarcerations.

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With the growing need for health promotion and drug use prevention services among backpackers, the Israel Anti-Drug Authority (IADA) established "The Backpackers' Project," focusing on drug use prevention, harm reduction, and unique health services and treatment targeting the young backpackers.

Two unique frameworks have been established with the aim to address this problem: the "Israeli Warm Home," which was established in India, as a collaboration between Israeli and Indian NGOs, in order to provide a first response to those affected by drug use, as well as prevention for those who have not yet been affected by it. The other framework is the establishment of "Kfar Izun" (Harmony Village), an innovative and unique recovery and rehabilitation center for young adults suffering from mental health problems due to the use of drugs, usually during backpacking trips.

121.1 Introduction

The post-army backpacking trip to Southeast Asia and South America has become a significant social phenomenon in the Israeli society over the past 20 years. According to the estimates of the Ministry of Foreign Affairs, close to 50,000 young Israelis go on backpacking trips each year, most of them for a duration between 3 and 12 months. Around 30,000 of them go to the Far East, usually to India (Bonny-Noach and Frish 2008; The Knesset Research and Information Center 2005).

For some young military veteran backpackers, the journey is a kind of "rite of passage," a way to disconnect and escape from the demands of society and a way to challenge themselves and their values (Bonny-Noach 2008a; Cohen 2003; Jacobson 1987; Mevorach 1996; Noy and Cohen 2005; Uriely et al. 2002). In a typical trip, the young backpacker is in a kind of moratorium stage – postponing the responsibilities expected in the adult world (Mevorach 1996) – like academic studies, finding and keeping a job, and building a family. Some develop "antiestablishment" viewpoints and "rebel against their parents'" generation.

Drug use is common among Israeli backpackers. The most commonly used drugs among backpackers are hallucinogens – cannabis products such as marijuana, hashish, Indian charas and hashish oil, hallucinogenic mushrooms, and LSD.

There are two main dangers for Israeli backpackers who use drugs. The first is getting into trouble with the local law, including getting arrested and imprisoned. In most cases they are ignorant of the local law. Sometimes they are sure that drug use is legal or feel that they are "above the local law." The second danger is the mental and physical damage that can occur due to drug use. An estimated 600 backpackers are seriously affected by drug use each year, some of them requiring hospitalization in psychiatric wards (Bonny-Noach 2008a, b; Knesset Research and Information Center 2005).

121.2 Treating Young ISRAELI Military Veterans with Dual-Diagnosis

121.2.1 The Backpackers' Project

The Israel Anti-Drug Authority (IADA) recognized the growing need for unique health promotion and prevention services for backpackers and established "The Backpackers' Project" in 1996, focusing on drug use prevention and harm reduction approach, providing tips for backpackers and information on what to do in case of emergencies. As part of the project, IADA distributed pamphlets containing information about the dangers of drug use. In 2002 IADA published an information booklet about the legal status of drug use in 39 countries that are popular travel destinations (Bonny 2002). In 2008 IADA published the book *Backpackers and Drug Abuse – A Documentary*, *Research*, *Treatment and Prevention Perspective* by Bonny-Noach Hagit. The book includes 26 chapters that portray a fascinating mix of backpackers' description documenting their experiences along with reports from scientific researcher.

In addition workshops organized by IADA for young combat soldiers prior to their release from the military presented the inherent dangers of drug use and its long-term consequences.

121.2.2 Treatment

Three unique frameworks have been established that aim to address the problem of drug use among backpackers.

121.2.3 The "Warm Home" in India

The establishment of the "Israeli warm home" in India is part of the attempt to prevent drug use and to treat young backpackers based on the concept of harm reduction. It serves as a place of meeting for Israeli backpackers and provides a range of activities and services, such as a library for borrowing books, the possibility to record Israeli music and to see movies, Internet and phone services, and other social activities to prevent drug abuse.

In case of emergency, offering immediate aid is a very important step which may significantly influence the likelihood of deterioration or improvement in the patient's condition and the likelihood of them developing mental disorders in the future. Backpackers affected by drug use are afraid of receiving treatment in a foreign place, using public services that do not always meet Western standards. Sometimes young backpackers who are found in a psychotic state are taken care of by their friends, who hide them and do not guide them to the necessary treatment they require.

When needed, they are rescued and brought back to Israel. So far the home has provided a first response to hundreds of backpackers in distress. The home is located in tourist centers, operating half of the year in Manali in the North and the other half of the year in Goa in the South, in accordance with the touring season.

121.2.4 Rescue

The Magnus International Search and Rescue is a private company which works closely with the Israel Anti-Drug Authority. The company locates travelers with whom contact has been lost for various reasons and works to reconnect them with their families, often within hours of receiving a request. When necessary, the company plans and carries out rescue operations at short notice while providing support and consultation for the families at home. A big part of the company's work is in aiding victims of drug use, particularly travelers suffering from drug-induced psychosis. After locating the travelers, they stabilize their condition, calm and reassure them, fly them back home, and guide them to continue treatment and rehabilitation.

121.2.5 Case Study: The Author (Mell) Accompanied a Rescue Operation from India

A few months ago, I accompanied Mr. Magnus (from Magnus International Search and Rescue) on a mission to bring back to Israel from Varanasi (India) a 21-year-old man who was in a psychotic state after massive use of charas (Indian hashish). The young man spoke freely with God, Moses, and Mohammed. He stood next to the Ganges River and threw his equipment and documents into the river as if he were saying goodbye to the world. He was spotted by four backpackers, who took care of him in a guesthouse. Despite not previously knowing him, they felt that it was their duty to help an Israeli in distress, and they contacted his parents. His parents requested our help in bringing him back home. When we arrived at the guesthouse, receiving directions from the four backpackers via their cell phone, they were very suspicious of us. During the 3 days, they took care of him, they identified with his psychosis, and it was harder to convince them than it was to convince the patient himself that we must take him with us – some kind of "folie à deux." Mr. Magnus told the patient, "don't worry, from now on I'll take care of all your needs," and gave him a fatherly hug and took him out of there. We transferred him to a proper hotel and made sure that he showered and dressed in clean familiar clothes that we had brought with us from his home and ate and drank and, most importantly, that he was able to sleep well with the help of benzodiazepines. This basic assistance significantly improved his condition. When a person experiences psychosis for the first time in his life, it leads to extreme anxiety. The fact that he did not sleep, eat, or shower properly enhanced his distress. Attending to his basic needs assisted in calming him down and in reducing the psychotic symptoms he was experiencing. I saw the craving for hashish in a new light when we arrived at the airport. Although we checked his

clothing and equipment while he was sleeping, a policeman who carried out a random check at the airport found two joints of hashish in his pocket. He confiscated them, put them in an ashtray nearby, and let us continue. The young man looked right and left and, the moment the policeman looked elsewhere, dashed over and grabbed the lost joints. I caught him by the arm, and for the first time in my life, I "hit a patient" – I shook his arm and threw away the joints and physically held him until we boarded the airplane. When we arrived in Israel, 36 h after meeting him, he was in a condition that did not require hospitalization – only a short period of ambulatory psychiatric treatment, with full remission.

121.2.6 Kfar Izun

Harmony Village (Kfar Izun) is an innovative and unique recovery and rehabilitation village for young adults suffering from mental health problems due to the use of drugs, usually during backpacking trips. The village was founded in 2001, on the beach near Cesarea. The village allows treatment without the need for registration and without the stigmas usually associated with treatment in psychiatric institutes. The uniqueness of the treatment provided at "Kfar Izun" is also reflected in the treatment environment – the village is located on the beach, in a relaxing and special surrounding. It is an "open village" both physically (no fence or security) and in terms of attitude. All patients come at their own will. The open village is an incentive to take responsibility for the situation, and the patients trust that they can take back control of their lives.

The village's therapeutic outlook meant that it was not possible to adopt the approach of treatment as an addiction, since the main problem here was not addiction. Thus, in terms of treatment received, two major decisions were taken: The first decision was to adopt the Salmon frontline treatment for the combat of stress reaction, which includes three treatment principles, immediacy, proximity, and expectations, and to combine it with methods of treating patients in distress, on the premise that most of the cases stemmed from a posttraumatic event and from distress, both for the patients and for their families. The second decision taken was to engage in self-learning all the time and make changes to the therapeutic concept if needed (Bonny-Noach and Frish 2008; Frish 2008).

121.2.6.1 Immediacy

One of the recommendations of "Kfar Izun" is that treatment begins immediately upon the patients' return from abroad and that the village is ready and equipped to receive patients immediately as they get off the airplane. This is not always implemented due to the skepticism of family members, who want to see firsthand the severity of the situation of their children.

121.2.6.2 Proximity

The village is located on the beachfront in an open surrounding, and the patients' rooms are similar to bungalows (similar conditions prevailed during the backpackers' trip).

In addition, the treatment staff (almost all of whom were once backpackers themselves) makes sure to recreate some of the environments and experiences from the backpacking trips.

121.2.6.3 Expectations

Each patient is told that the crisis experienced is temporary and will pass quickly and they will return to normalcy after a period at the village. The presence of other patients who went through similar experiences is a very meaningful and important source of support. The other patients are proof that they are not the only one suffering from such a crisis and recovery is possible. Also, the limited treatment period helps patients realize that they are expected during this period to succeed and to function normally and that their current condition will not last forever.

The professional staff includes psychiatrists, psychologists, and social workers. In addition to conventional treatment (group therapy, individual therapy, family therapy, and psychiatric pharmacologic treatment[1]), there is also some oriental therapy, body psychotherapy, naturopath, nutrition therapy, and reflexology.

An evaluation research, both quantitative and qualitative, of "Kfar Izun" (Ezrahi et al. 2006) showed that the success rate of patients treated at the Harmony Village was high. Success was measured at several levels: 24 % recuperated and left the village without visible pathological symptoms; 31 % were diagnosed as having mental illnesses in remission; 39 % showed a slight improvement in their psychiatric condition; 6 % showed no improvement. The qualitative research findings compared graduates of the village (up to 6 years) and a control group and found lower clinical states of mental stability in the control group than in the graduates group. The functional-behavioral findings showed that most of the graduates returned to an independent lifestyle, which includes integration in the work force or having high education, development of long-term plans, and setting of normative targets in comparison to their peers. It was also shown that many patients keep in touch with the village's staff, and it is clear that most of them have returned to a normative and productive lifestyle.

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Psychotic Disorders and Substance Use Disorders

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Contents

Abstract

The comorbidity of psychotic and substance use disorders (SUDs) is a major issue in mental health because of its high frequency and poor prognosis. Moreover, it is often neglected both for the difficulty to assess SUDs in psychotic patients and for scarce attitude to evaluate and treat substance misuse by psychiatric service staff. On the other hand, psychotic patients with SUDs can receive inadequate treatment for psychosis by SUD services for similar reasons.

Assessing and treating this comorbidity require the knowledge and the integration of specific tools and interventions that should be tailored toward patients' clinical condition and that can be difficult to manage in daily clinical practice.

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122.1 Introduction

Since the 1980s the literature has gradually shown how the care of mental illness has frequently to deal with the coexistence of substance use disorders (SUDs), namely, abuse or dependence, and other mental disorders, a situation usually defined as "dual diagnosis " or "comorbidity" (Kessler 2004). Dual diagnosis is a case of heterotypic comorbidity, that is, the simultaneous presence of mental disorders belonging to different clusters, while homotypic one can be defined as the coexistence of two or more disorders within the same diagnostic cluster, e.g., a cannabis use disorder and an alcohol use disorder (Angold et al. 1999).

The relevance of dual diagnosis lies in its high prevalence, at least for some settings, and its detrimental effects on response to treatment and clinical and social outcomes, which are worse than in patients affected by a single diagnosis (Morojele et al. 2012).

Dual diagnosis may include any mental disorder and any SUDs, therefore an extremely broad and various condition. However, some authors have restricted their interest to situations where a substance misuse accompanies the most severe mental disorders, such as schizophrenia or bipolar disorder (Carrà et al. 2012). SUDs are the most frequent comorbidity among psychotic disorders and can further dramatically worsen an unfavorable prognosis (Wright et al. 2000).

122.2 The Comorbidity of Psychotic Disorders and Substance Use Disorders

122.2.1 Epidemiology

122.2.1.1 The USA

In the USA, about 25 % of the general population has suffered from a mental disorder in the last 12 months. Among them, the three main psychotic disorders, namely, schizophrenia, delusional, and schizoaffective disorder, seem to have a prevalence of about 1–2 % (Reeves et al. 2011; West 2008).

SUDs are more common than psychoses. In 2011, according to the National Survey on Drug Use and Health (NSDUH), 8 % of the general population over 12 years of age resulted suffering from an SUD. Among them, 5.5 % suffered from an alcohol use disorder, 1.5 % had another SUD, and 1 % had both (SAMHSA 2012). The most frequently abused substances were alcohol, marijuana, analgesics, cocaine, and heroin.

Evidence about the prevalence of dual diagnosis among people with psychotic disorders in the US general adult population comes from three large studies, the Epidemiologic Catchment Area (ECA) study, the National Comorbidity Survey (NCS), and the National Epidemiological Survey of Alcohol and Related Conditions (NESARC).

The ECA study was carried out between 1980 and 1984 on a sample of more than 20,000 subjects aged over 18 years and found that among individuals with schizophrenia, SUDs had a prevalence of 47 % (odds ratio $= 4.6$, $p < 0.001$).

Indeed, 34 % of subjects had an alcohol use disorder (OR = 3.3, $p < 0.001$), and 28 % a drug use disorder (OR = 6.2, $p < 0.001$ – Regier et al. 1990). Conversely, comorbid schizophrenia was found in 3.8 % of subjects with an alcohol use disorder and 6.8 % of those with a drug use disorder (Regier et al. 1990). The NCS study was conducted between 1990 and 1992, on a sample of approximately 8,100 individuals between 15 and 54 years of age, and found a prevalence of SUDs of 44.8 % among those suffering from chronic psychotic disorders (Kessler et al. 1996). Finally, the NESARC study interviewed more than 40,000 noninstitutionalized adults in 2000–2001, finding that psychotic disorders have a prevalence of 1.5 % among people affected by alcohol use disorders and of 4.2% among people suffering from substance use disorders (Lev-Ran et al. 2012).

Smaller surveys show prevalence rates between 20 % and 65 % among people suffering from a severe mental illness (including psychosis), depending on geography, service setting, population composition, and evaluation tools (Cuffel and Chase 1994; Drake et al. 1989; Carrà and Johnson 2009). The prevalence of psychotic disorders among substance users is lower: according to the NESARC study, prevalence is less than 10 %, and generally comorbid schizophrenia is rare among opioid users in addiction services (Kidorf et al. 2004). However, there are some differences among users of specific substances. The prevalence among inhalant users is an exception, with 20 % of them affected by psychosis (Lev-Ran et al. 2012). These differences about the prevalence of psychosis among substance users may reflect the complex etiology of dual diagnosis.

122.2.1.2 Europe

European evidence about psychotic and substance use disorders show prevalence rates in the general population of about 1 % and between 0.3 % and 3 %, respectively (Wittchen et al. 2011; Eurostat 2011). The most commonly abused substances are alcohol and cannabis (Wittchen et al. 2011). In Europe, unlike in the USA, there are no studies that routinely and comprehensively investigate the prevalence of dual diagnosis across all the countries. However, the European Schizophrenia Cohort (EuroSC), a multicenter prospective study carried out in Europe on a cohort of 1,200 patients with schizophrenia, found a prevalence rate of 24 % for comorbid substance dependence mostly due to alcohol, albeit with some differences among the countries in which the study was carried out. Dual diagnosis had a prevalence rate of 35 % in the UK, 21 % in Germany, and 19 % in France (Carrà et al. 2012). Smaller studies have shown similar prevalence rates across European countries. Moreover, according to various local studies, psychotic disorders have a prevalence of about 5–15 % among individuals affected by SUDs (Carrà and Johnson 2009; Gual 2007).

In summary, in Europe prevalence rates of substance misuse among people with psychotic disorders seem to be lower than in the USA (Carrà et al. 2012). The differences between USA and Europe may, at least partly, depend on important differences in lifestyle and care pathways of populations surveyed. Thus, there is the need of a prudential approach in interpreting these data, as the epidemiology of dual diagnosis depends upon many factors, which may vary across different countries. Evidence must be interpreted taking into account local settings' features.

122.2.1.3 Critical Issues of Dual Diagnosis Epidemiological Studies

Most of the studies on comorbidity of psychotic and substance use disorders deal only with schizophrenia, neglecting other psychoses, so very fragmented relevant evidence is available for the latter (Wittchen et al. 2011). Furthermore, most of the evidence on dual diagnosis comes from the USA, which limits its generalizability, because of the organizational features of their health-care system that influence its accessibility. Moreover, available epidemiological studies on dual diagnosis have shown various methodological limitations.

First, it must be considered that the recruitment of people with "dual diagnosis" may not be so obvious: the assessment techniques show variable validity (Dixon 1999). Second, it is common to merge categories of dependence and abuse (Weaver et al. 2001). Although this can be useful for rough estimates of dual diagnosis prevalence, it makes difficult to achieve accurate data.

There are also issues regarding the recruitment of samples: convenience samples help to ascertain and explain the critical aspects of treating specific population, but they may provide misleading findings about the real prevalence of dual diagnosis. It is well known that dual diagnosis is significantly more common among some special populations, e.g., patients admitted to acute psychiatric settings, homeless, and users of the criminal justice system (Winklbaur et al. 2006). Finally, two interrelated problems must be taken into account: the spread of polysubstance abuse, including alcohol, and the difficulties in ascertaining a problematic substance use. Polyabuse is particularly common among patients suffering from psychotic disorders (Weaver et al. 2001; Dixon 1999; Drake et al. 1993), so each patient might have more than one SUD, making almost impossible distinguishing them. Moreover, patients often deliberately hide their consumption of substances, leading to an underestimation of their prevalence (Kavanagh et al. 2002).

As a whole, the epidemiological research about dual diagnosis shows many uncertainties, partly due to organizational problems and partly due to the very nature of the patients. In fact, psychotic disorders and SUDs are severe illnesses, and suffering from these conditions makes people exposed to several confounding factors, which can hamper validity of correlations and causal links. However, an epidemiological understanding is needed in order to implement appropriate treatment programs.

122.2.2 Potential Etiological Relationships Among Psychotic and Substance Use Disorders

Substance use and psychotic disorders seem to be linked by a mutual risk relationship (Morojele et al. 2012; Brady and Sinha 2005). Their strong epidemiological, biological, and clinical association has worked as a springboard for a large number of research initiatives aimed at understanding the etiology of this association. The efforts have been mainly directed in ascertaining if one has a significant role in the etiology of the other. Furthermore, some authors have hypothesized that both these disorders may be due, at least partly, to a common cause (Volkow 2009).

However, there are no firm conclusions about any etiological links between SUDs and psychosis, even if various risk factors for dual diagnosis have been found, and some etiological models have been developed.

122.2.2.1 Correlates and Risk Factors for Dual Diagnosis

Genetics

It is known that both SUDs and psychotic disorders have their own genetic risk factors, namely, a polygenic inheritability with multiple genes giving each one a small contribution to the global risk of developing these diseases (Kirow and Owen 2009; Strain and Anthony 2009).

Genetics account for about 30–60 % of the risk of developing an SUD. The genes' contribution in the etiology of psychotic disorders is less clear, even if some authors state that genes can account for up to 80 % of the risk for schizophrenia (McCann and Ricaurte 2009; Sullivan et al. 2003).

Until a few years ago, it was thought that vulnerability to SUDs and psychosis depended on distinct mechanisms of inheritance (Krystal et al. 2006). However, more recently some genes have been identified as contributing to the pathogenesis of both disorders. Among others, there are various genes coding for factors involved in brain development and in neuronal plasticity, such as the genes for neuregulin-1 (NRG1), some neurexins (NRXN1 and NRXN3), the catechol-O-methyltransferase (COMT), and the monoamine oxidase A (MAOA – Volkow 2009).

Male Sex and Young Age

These characteristics are strongly associated with comorbid psychotic and substance use disorders. However, in clinical practice it is recommended not to neglect the search for substance misuse among women and the elderly, since this condition is often overlooked, with poor treatment outcomes (Winklbaur et al. 2006; Kavanagh et al. 2002; Dixon 1999).

Low Educational Level and Unemployment

According to various studies, these factors are associated with both conditions (Volkow 2009), probably because they favor drift toward social relationships and situation with high risk of substance consumption (Palomo et al. 2007).

Substance Availability and Attitude Toward Substance Consumption

Living in social contexts characterized by high availability of substances and belonging to a social network familiar with consumption seem to favor its spread among individuals with psychotic disorders (Kavanagh et al. 2002). It seems that these factors are among the main determinants of patients' patterns of consumption (Dixon 1999).

Personality and Childhood Disorders

These conditions may predispose to a problematic substance use (Krystal et al. 1999). They include two dimensions of personality, sensation seeking and sociopathy. Sensation seeking is defined as a temperamental dimension characterized by impulsive search for gratification and poor tolerance toward frustration (Cloninger and

Svrakic 2009). Sociopathy is a dimensional connotation of personality characterized by greed for personal advantage and gratification, especially at the expense of others, through manipulation or violence; lack of empathy; inability to plan long-term behaviors; disregard for the safety or health of themselves or others (APA 2000). Moreover, a childhood history of attention-deficit/hyperactivity disorder (ADHD) has been correlated with a high prevalence of dual diagnosis (Drake et al. 1993).

Early Onset of Illness and Good Premorbid Functioning

An early onset of psychosis is generally associated with a poorer premorbid functioning. However, dual diagnosis seems assciated with both an early onset of illness and a good premorbid functiong. The reasons of this epidemiological evidence are not yet clear. Some authors have hypothesized that subjects affected by dual diagnosis probably would have had a later onset of psychosis, which is associated with a good premorbid functioning, but the exposure to drugs has anticipated its onset (Dixon 1999).

Subthreshold Symptoms Among Substance Users

It is well known that subclinical psychotic symptoms are risk factors for subsequent onset of psychotic disorders (Van Os and Allardyce 2009). Furthermore, subclinical psychotic symptoms increase the risk of substance consumption (Rietdijk et al. 2011). Therefore, prodromal manifestation of psychosis could be risk factors both for chronic psychotic disorders and SUDS.

In summary, it seems that the SUDs and psychotic disorders share many genetic and psychosocial risk factors (Volkow 2009). In addition, the risk factors associated with dual diagnosis are largely similar to those for the pathological consumption of substances found in the general population (Strain and Anthony 2009).

122.2.2.2 Etiopathogenesis: Models and Evidence

The Self-Medication Model

An intriguing hypothesis proposes that self-medication by substance abuse is a coping attempt by people with schizophrenia, matching the pharmacological properties of substances with the particular psychiatric symptoms and states experienced (Khantzian 1985, 1997). However, this should imply diagnostic and symptomatological differences in substance selection between individuals suffering from psychosis and the general population (e.g., choice of stimulants and negative symptoms should be associated). Neither prediction is supported by research evidence. Among people suffering from schizophrenia, no replicable patterns of substances chosen and symptoms experienced have been identified. Substance consumption pattern is actually similar to that found in other diagnostic groups (e.g., El-Guebaly and Hodgins 1992) and reflects the substance use pattern found in the general population where the sampling took place (Palomo et al. 2007; Krystal et al. 2006). As a matter of fact, given the frequent occurrence of multiple substance misuse as discussed above, it is not possible to attribute any observed symptomatological and clinical difference to a single drug class. The only strong evidence is that regarding the association between fewer negative symptoms and dual

diagnosis, though it is not still clear whether this may involve lifespan or just current misuse (see Potvin et al. 2006 for a review). However, a less definitive form of the self-medication hypothesis that does have some supporting evidence suggests that substances are used to relieve dysphoria and anxiety and to alleviate tension (Krystal et al. 2006; Addington and Duchak 1997) rather than medicating core psychotic symptoms.

However, some neurobiological evidence might support the self-medication hypothesis. For example, nicotine dependence (which affects about 70 % of schizophrenic individuals) may determine an improvement of cholinergic neurotransmission to the nicotinic receptors, whose function has proven to be impaired in schizophrenia. It may also increase the expression of glutamate decarboxylase, with a consequent increase in GABAergic activity, also reduced in this disorder. These ultrastructural effects will be the biological substrates of the improvement in cognitive performances observed among nicotine-dependent people with schizophrenia, especially for working memory and selective attention (Volkow 2009; Winklbaur et al. 2006).

Furthermore, cocaine would alleviate some symptoms associated with psychotic disorders, first of all the extrapyramidal effects of antipsychotics, because of its action as dopamine reuptake inhibitor. Cocaine may also have a role in balancing the low functioning of the reward circuit observed in schizophrenia, which could be further worsened by high-power antipsychotics (i.e., haloperidol). The hypothesis seems to be supported by some evidence, although limited, about the beneficial effects of atypical antipsychotics in the treatment of psychotic disorders comorbid with substance misuse (Brady and Sinha 2005). This may be due to the lower dopaminergic activity of the second-generation neuroleptics (Volkow 2009; Winklbaur et al. 2006). Finally, cocaine and other drugs of abuse may have the effect of enhancing receptivity for glutamate in the nucleus accumbens (NA), through an increase in the expression of AMPA-type receptors, helping to offset the glutamatergic hypofunction recently observed in schizophrenia (Palomo et al. 2007).

Although confirmed by various studies, the self-medication hypothesis does not seem entirely convincing. If we accept this hypothesis, it should be possible to observe patterns of substance use typical of schizophrenia, adopted by dual diagnosed users to cope with specific symptoms. However, patterns of consumption among people with psychotic disorders are not different from those adopted by the social context to which they belong (Palomo et al. 2007; Krystal et al. 2006).

Furthermore, it has been argued that if drugs of abuse improved the symptoms, probably the prognosis of patients with dual diagnosis would be better, but the literature is almost unanimous in affirming this is not the case (Palomo et al. 2007). However, it could be possible to rebut that, given the deficit in planning long-term actions, people with schizophrenia might choose the temporary benefit of a substance effect at the expense of broader and less immediate negative impact on their lives (D'Souza et al. 2009).

To conclude, there is insufficient evidence to conclude that patients with psychosis are more exposed to substance use disorders only because of their willing to self-medicate their symptoms.

Environmental Stress Vulnerability

According to this model, the problematic use of substances would be one of many factors that can precipitate the development and exacerbation of psychotic disorders in susceptible individuals (Winklbaur et al. 2006). Alcohol, cannabis, and methamphetamines have been proved capable of causing persistent psychoses, along with transient psychotic syndromes (Ross and Peselow 2012). However, this model seems simplistic, as several studies have reported that psychotic disorders are not merely caused by SUDs, given the mutual risk relationship that seems to bind these two syndromes (Volkow 2009).

Vulnerability to Comorbid Dependence

In this model, suffering from a psychotic disorder is per se a risk for substance use disorders, as both illnesses may share various biological substrates. The model is supported by evidence at various levels. Individuals affected by schizophrenia seem to have a lower capacity of anticipating and counteracting the negative consequences of their substance use and to avoid offers of drugs and exposure to associated conditions due to their poor social skills (Palomo et al. 2007; Kavanagh et al. 2002). The main neurobiological evidence in favor of this model comes from the reward system and its connections. First, positive symptoms of schizophrenia have been correlated with an increased activity of the dopaminergic projections going from the mesencephalic ventro-tegmental area (VTA) to NA, the so-called reward system. However, an increase in the activity of this pathway is also the biological substrate of the positive reinforcing properties of any substances, so its hyperactivity could increase the risk of both psychotic symptoms and substance use relapse (Chambers et al. 2001). Second, schizophrenia and substance use disorders may both cause a decrease in the activity of efferent projections from the prefrontal cortex and the hippocampus to the NA. These fibers usually counteract excessive signaling from the reward way. In schizophrenia there is possibly a developmental abnormality in prefrontal cortex and hippocampus, which may result in a deficit of these projections. Furthermore, hyperactivity of the reward system can inhibit their activity, in case of activation of this way due to substance consumption. So both psychoses and substance use disorders can hamper the physiological inhibition of dopaminergic signaling in the NA, which results in a diathesis toward psychotic relapses and substance consumption (Ross and Peselow 2012).

A further suggestion of a common substrate for psychoses and SUDs comes from various studies of functional magnetic resonance imaging that have demonstrated that patients with SUDs and schizophrenia have a reduced activation of NA during the anticipation of reward cues. Moreover, the magnitude of this deficit of activation seems correlated to the severity of their negative symptoms (Krystal et al. 2006).

When evaluating the etiological models of dual diagnosis, it is important to keep in mind that these hypotheses probably describe only some of its facets, so they should not be conceived as mutually exclusive. For instance, attempts to self-medicate psychotic or unspecific symptoms could be reinforcing elements for substance consumption, and people with schizophrenia may be highly vulnerable to

such reinforcement. It is also possible that pathogenesis mechanisms shared by all or most of the drugs of abuse coexist with mechanisms related only to specific psychotropic substances (Volkow 2009).

122.2.2.3 Cannabis and Psychotic Disorders

In the last 20 years, a body of evidence has accumulated that shows that cannabis can cause, in a dose-dependent manner, psychotic symptoms, psychotic relapses, and the onset of chronic psychotic disorders, sometimes clinically diagnosable as schizophrenia (Bossong and Niesink 2010; Moore et al. 2007). Some studies also support the evidence that the age of onset of psychotic disorders is earlier in those with a cannabis-related disorder (Large et al. 2011).

However, there are also different evidences. Sevy and colleagues (2010) state that the difference in the age of onset of chronic psychosis between patients with cannabis use disorder and patients without it may not be related to cannabis use but to demographic and clinical variables, namely, male gender, lower socioeconomic status, better premorbid childhood social adjustment, and more severe positive symptoms. Other authors state that earlier age of onset of psychotic symptoms in cannabis users is not due to an etiological role of cannabis, but to the fact that cannabis use is common among young people. So, the results observed might have been due to the recruitment bias of people in which the psychotic illness started earlier by itself (Wade 2005). However, it is unlikely that cannabis causes by itself schizophrenia *ex novo*. Some statistical models have been developed showing that the use of cannabis can only precipitate psychosis in people who would have however developed the disease and that cannabis can worsen the course of this disorder (Degenhardt et al. 2003). Furthermore, it has been claimed that if cannabis could cause schizophrenia, the observed increase of cannabis use, for example, in Australia, where the study was run, would have gone together with an increase in prevalence of schizophrenia, which was not observed (Degenhardt et al. 2003). However, it has been argued that the onset of schizophrenia can occur many years after the exposure to cannabis, so being difficult to be simultaneously detected (Moore et al. 2007).

The debate about the relationship between cannabis and psychosis has been up and running in the last few years, also because of many methodological issues that make difficult to test a clear research hypothesis, such as the number of related confounders.

Two recent systematic reviews added evidence about the etiological role of cannabis in the pathogenesis of psychotic symptoms and disorders. Moore and colleagues (2007) found an increase in incidence of psychotic symptoms and disorders in cannabis users, with odds ratio ranging from 1.41 (CI 95 %: 1.20–1.65) to 2.09 (CI 95 %: 1.54–2.84) in a dose-dependent manner.

Large and colleagues showed in another systematic review that cannabis and other illicit substances are associated with earlier onset of psychosis. This relationship was not demonstrated for alcohol and psychosis. More in detail, cannabis users experienced an onset of psychosis 2.7 years earlier than non-cannabis users (Large et al. 2011).

The psychotogenic properties of cannabis are also supported by neurobiological data about both delta-9-tetrahydrocannabinol (THC), which is the main psychoactive component in cannabis (Bossong and Niesink 2010), and the two most important endogenous cannabinoids, namely, anandamide and 2-arachidonoylglycerol.

There is some evidence about the property of THC facilitating dopaminergic neurotransmission from the mesencephalic ventro-tegmental area (VTA) to the nucleus striatum. Animal studies have shown that cannabinoids are released by dopaminergic neurons of the VTA and act on type 1 endocannabinoid receptors (CB1) on the glutamatergic and GABAergic neurons that modulate the dopaminergic neurons. This results in a decrease in their activity and a consequent increase in the dopaminergic firing from the VTA to the striatum, which has been correlated to positive psychotic symptoms (hallucinations, delusions, disordered thought, and behavior). Cannabinoids are also involved, together with dopamine, in the phenomena of long-term depression and long-term potentiation of neural projections from the cortex to the striatum (Bossong and Niesink 2010; Kuepper et al. 2010). The former have been correlated with the development of psychotic symptoms (Kuepper et al. 2010; D'Souza et al. 2009). THC may also influence projections from VTA to the prefrontal cortex, where they could acutely induce an increase in dopamine. However, chronic administration of THC seems to cause a chronic decrease in prefrontal dopamine, and both an excessive increase and decrease of prefrontal dopamine have been associated with a cognitive impairment, for instance, in attention and memory, which is typical of negative and cognitive symptoms of schizophrenia (Kuepper et al. 2010; D'Souza et al. 2009). Furthermore, carriers of an allele of the catechol-O-methyltransferase (COMT) gene with a valine instead of a methionine at the codon 158 (val158met) have shown more proneness to the psychotic and cognitive effects of cannabis. This polymorphism causes an increase in the activity of COMT, which results in a decrease in prefrontal dopamine levels (Kuepper et al. 2010).

THC may also act on the CB1 receptor on GABAergic interneurons to reduce their activity, which could result in a loss of their inhibitory activity on pyramidal cells, causing a loss of coordination in their activity. Other studies revealed that cannabinoids may reduce the glutamatergic synaptic transmission in several brain regions, such as the hippocampus, the prefrontal cortex, the NA, and the amygdala (D'Souza et al. 2009). The reduced GABAergic and glutamatergic activity caused by cannabinoids resembles what is observed in schizophrenia, even if its meaning is still poorly known (Moore et al. 2007).

More generally, Bossong and Niesink (2010) formulated two hypotheses about the role of cannabis in psychotic disorders. Recent findings show that the CB1 receptor is very important for a correct brain development, mainly during adolescence, a period in which the development of neural circuits for superior brain functions is completed. A heavy exposure to exogenous cannabinoids may disturb this process, causing alterations in local neural circuits that might result in schizophrenia. Evidence about the hazard of cannabis for neural development comes from a recent meta-analysis of 14 studies about brain abnormalities in nonpsychotic cannabis users. Analyses have shown that cannabinoid consumption is associated

with a significant reduction in hippocampal gray matter, which could be critical during adolescence, as it may compromise the last phases of neural development, so having effects on cognitive functions (Rocchetti et al. 2013). Another hypothesis considers exogenous cannabinoids, altering perception and memory, which might block or alter the perception of exogenous stimuli, relevant for brain maturation in adolescence.

In summary, many studies, both in vivo and in vitro, on animals and humans, confirm that exogenous cannabinoids can interfere with the physiological brain activity and cause pathological processes very similar to the ones observed in psychotic disorders. However, many results have not been confirmed by subsequent studies, making still largely unknown the real impact of cannabinoids on the brain (Volkow 2009).

Thus, current evidence about the relationship between cannabis and psychosis shows that cannabis can cause transient psychotic positive, negative, and cognitive symptoms in a dose-dependent manner, besides unspecific symptoms such as anxiety (D'Souza et al. 2009), and can cause a relapse of chronic psychotic disorders (Kuepper et al. 2010; Moore et al. 2007). However, cannabis seems to be neither a necessary nor a sufficient cause for the onset of chronic psychotic disorders. It is one of the many factors, partly known and partly unknown, that interact to give each person a specific risk for chronic psychosis (Bossong and Niesink 2010; Kuepper et al. 2010; D'Souza et al. 2009; Volkow 2009). Thus, preventing or reducing the use of cannabinoids is useful to delay or maybe avoid the onset of psychotic disorders, especially in people at high risk. It is also important to give such an advice to pregnant women, due to the lipophilic structure of exogenous cannabinoids and the evidence about their detrimental effect on the neural development. In fact, even if the onset of psychosis were inevitable, delaying the onset could allow many patients to reach a developmental level sufficient to have a decent life (Large et al. 2011).

122.2.3 Clinical Features, Course of Illness, and Diagnosis

122.2.3.1 Clinical Features and Course of Illness

Clinical pictures of comorbid psychotic and substance use disorders are complex and difficult to be assessed (Morojele et al. 2012). Both disorders may be exacerbated by exposure to environmental stressors and can worsen each other, both in the short and the long term (Ross and Peselow 2012; Volkow 2009; Brady and Sinha 2005).

In clinical practice, patients can be affected by both a psychotic disorder and an SUD, but their psychotic symptoms may also be manifestations of a substance-induced psychosis (SIP). This term describes psychotic syndromes due to substance use, abuse, intoxication, and withdrawal. Furthermore, a patient can have both a primary psychotic disorder and an SIP (Center for Substance Abuse Treatment 2005).

In case of an SIP, signs and symptoms are usually not as bizarre and complex as the ones seen in schizophrenia and other primary psychotic disorders, and they will persist for days and weeks from the cessation of substance consumption

(Keshavan and Kaneko 2013; CSAT 2005). Therefore, longitudinal observation is of primary importance to differentiate a situation of comorbidity from a substance-induced disorder, because it can be objectively impossible to distinguish a psychosis in a substance user from an SIP. It is also possible that people develop psychotic disorders as a consequence of heavy and prolonged substance consumption, but psychotic disorders may last for several months and years or also lifelong even after the cessation of the substance use. This has been observed for cannabis (Niemi-Pynttäri et al. 2013) and methamphetamines (Grant et al. 2012; CSAT 2005). Also several years of alcohol dependence, especially after various episode of acute withdrawal (delirium tremens), can induce a persisting psychosis (Ross and Peselow 2012).

Any substance, if taken in large quantities and over a long enough period can induce a psychotic state (CSAT 2005). It is also important to know that even low levels of substance use can induce a psychotic relapse (CSAT 2005). However, the clearest psychotogenic effect has been shown for stimulants, such as amphetamine and cocaine, cannabis, and NMDA antagonist hallucinogens, such as phencyclidine and ketamine. Also lysergic acid diethylamide (LSD) and 3,4-methylenedioxy-N-methylamphetamine (MDMA) can cause hallucinations, but usually only during acute intoxications. Alcohol and benzodiazepines can induce psychotic symptoms only in acute withdrawal states, while opiates and nicotine have not clearly shown psychotogenic properties (Keshavan and Kaneko 2013). Alcohol, cannabis, and cocaine are the most frequently abused substance by dually diagnosed patient, but especially because of the high prevalence of polysubstance use, it is important not to exclude the hypothesis of concurrent different drugs (Weaver et al. 2001; Dixon 1999; Drake et al. 1993).

People with psychosis who misuse substances may be different from the abstinent ones in frequency and intensity of positive, negative, and cognitive symptomatology. There is evidence about a higher frequency of positive symptoms, with less negative and cognitive symptoms, in those with substance use disorders (Harrison et al. 2008; Kavanagh et al. 2002; Soyka et al. 2001; Dixon 1999).

Neuromaging studies have shown that heavy and ongoing alcohol, cannabis, and methamphetamine abuse increases the cortical thinning seen in schizophrenia, especially in the prefrontal and temporal cortex, maybe worsening the progressive deficit of the executive functioning observed in psychosis (Aoki et al. 2013; Large et al. 2011; Winklbaur et al. 2006).

Dually diagnosed people are prone to adverse outcomes in several domains. Clinically, they have a high risk of treatment noncompliance, poor clinical response, more frequent psychotic relapse and hospitalization, violent behavior, suicide attempts, and medical problems, such as infectious diseases, so being frequent users of emergency services (Drake et al. 2004; Noordsy and Green 2003). They also face some adverse social and economic outcomes. They are in fact more at risk of victimization, housing instability and homelessness, unemployment and poverty, and committing offences with related criminal justice issues (Kavanagh et al. 2002; Dixon 1999). Besides, dual diagnosis imposes a high emotional and economic burden on families and friends of patients, increasing the risk of social drift (Ross and Peselow 2012; Kavanagh et al. 2002; Alverson et al. 2000; Dixon 1999).

122.2.3.2 Assessment

The assessment process has obvious consequences in terms of treatment and prognosis.

An adequate assessment starts from clinical suspicion. Cues of a history of substance abuse can be found in risk factors described above or in a childhood history of attention-deficit disorder (Drake et al. 1993). Moreover, because of the high prevalence of comorbid severe mental illnesses and substance use disorders, the presence of one of them should be considered by itself a reason to search for the other (Ross and Peselow 2012; Morojele et al. 2012).

The assessment can be very difficult for various reasons, especially in emergency settings. Patients' clinical conditions may be very complex, and their cooperation is not warranted, for instance, because of agitated or violent behavior, disorganized speech, high sedation or paranoid psychotic symptoms, acute or chronic cognitive impairment. Besides, the patient may not want to talk about his symptoms or his substance use because of embarrassment, fear of negative responses, or scarce insight (Kavanagh et al. 2002). Therefore, it could happen that the clinician has to achieve a diagnosis based only on scarce and fragmentary data.

To date, there are various tools to clarify a comorbid clinical picture. The most adequate approach consists of combining two or more of them. More in detail, clinical history, physical examination, clinical interview, laboratory tests, and neuroimaging should be used together to obtain the most reliable information (Ross and Peselow 2012).

First of all, it is essential to establish a positive therapeutic alliance between the clinician and the patient, setting a nonjudgmental and trustful relationship (Alverson et al. 2000; Drake et al. 1993). The clinical history can be evaluated by asking the patient. It is important to ascertain if he has ever attended psychiatric services or has ever received a psychiatric diagnosis or has been prescribed a psychopharmacological treatment. Likewise, the clinician must ask about any psychotropic substance consumption, substance use disorder, or related treatment. If the patient assumes substances, it is important to know what substances, or at least what substances the patient believes to assume, as well as quantity and frequency of consumption (Morojele et al. 2012). Besides, the patient's last drug consumption time is very important for diagnostic assessment, especially in case of emergency (National Collaboratory Centre for Mental Health 2011). If more reliable information is needed, the clinician should ask patients' collaterals, such as family members, friends, or partners. However, it is important to keep in mind that even patients' collaterals can be unreliable, for various reasons. They can be interested in hiding the patients' drug consumption, for example, because of legal reasons, or they simply may not know how the patient lives.

The clinical interview can be integrated with structured interviews or questionnaires. They have been found to produce highly reliable diagnoses (Dixon 1999), but they must be tailored toward the patient's clinical conditions. The following tests have shown adequate reliability: for patients with higher functioning and less severe mental illness, the Addiction Severity Index (ASI) and the Drug Abuse Screening Test (DAST) and, for alcohol use disorder, the CAGE and the Alcohol Use Disorders Identification Test (Ross and Peselow 2012; Morojele et al. 2012).

However, these instruments may not be reliable for patients with the most severe mental illnesses, for two reasons. First, these tools focus on substance-related dysfunction, of which the most severely ill patients could not be aware. Second, they may not be sensitive to the cognitive impairment common among the most ill patients (Ross and Peselow 2012). Two screening tools developed for such patients are the Dartmouth Assessment of Lifestyle Instrument and the Substance Use Event Survey for Severe Mental Illness. Regardless of which screening tool will be chosen, it is important to verify if it can be easily administered to a patient and if it has been validated for dually diagnosed populations (Samet et al. 2004). Furthermore, these instruments should be used when the patient is stabilized, and using too lengthy self-report tools should be avoided. Repeating the administration of these tools may also help to assess variations in the course of substance disorders or mental illnesses (Drake et al. 1993).

The physical examination is as important as clinical history, and every sign or symptom must be evaluated (Keshavan and Kaneko 2013). Its main purpose, besides looking for any condition that deserves medical or surgical treatment, is to search for the physical stigmata of a drug use disorder or of a mental illness. Cues of a substance use disorder can be signs of intoxication, withdrawal, or chronic use, but they can overlap each other and with signs of comorbid physical illnesses and unspecific vegetative symptoms (i.e., tachycardia and diaphoresis because of anxiety – Morojele et al. 2012). The clinician should search for signs useful to unmask intoxication or withdrawal syndromes. Signs and symptoms of intoxication and withdrawal by psychotropic substances are described elsewhere in this book. Here, the importance of evaluating if the patients' behavior suggests delusions or hallucinations and if there are physical signs of activation or inhibition, including pupils' diameter, will only be stressed. Besides, a horizontal, vertical, or rotary nystagmus can suggest NMDA receptors antagonist intoxication, such as phencyclidine or ketamine (Keshavan and Kaneko 2013; Ross and Peselow 2012). Also the chronic stigmata of a substance use disorder must be searched for, such as signs of cirrhosis or of intravenous drugs use (Ross and Peselow 2012). A poor nutritional state could be observed in case both of an SUD and of different severe mental illness.

Laboratory tests provide objective evidence of substance consumption, as well as signs of medical illness or somatic consequences of drug use. Urine tests are a cost-effective tool to assess drug consumption. They usually detect drugs taken in the last 48 h before the test. THC is an exception: due to its lipophilic structure, it can be stored in fat cells and found in urine samples for up to 6 weeks after consumption. Other instruments include breath analysis for alcohol, which can detect consumption only in the last few hours before the test, and plasmatic blood levels, useful to detect many substances of abuse. Blood cells, liver function, and carbohydrate-deficient transferrin (CDT) are indirect measures of alcohol consumption (Ross and Peselow 2012; Drake et al. 1993). Also the hair radioimmunoassay can be useful (Ross and Peselow 2012).

Finally, structural neuroimaging, such as computed tomography (CT) or magnetic resonance imaging (MRI), could be useful to exclude an organic etiology of neuropsychiatric signs and symptoms (Keshavan and Kaneko 2013).

In summary, diagnosing a primary psychosis, a psychosis due to substances or organic disease, or a condition with comorbid psychotic and substance use disorders can be challenging. It requires a holistic, integrated approach that must be tailored toward patients' conditions, setting, and available tools.

Overlooking one of these conditions or incorrectly assuming multiple diagnoses can, respectively, affect the prognosis or lead to unnecessary treatment and iatrogenic harm (Ross and Peselow 2012).

122.2.4 Treatment and Prognostic Issues

Treating people with comorbid psychosis and substance-related disorders can be very difficult. It can follow a sequential, a parallel, or an integrated approach. The sequential treatment takes care of one disorder at a time, from the first to the second once that the former is stable or in remission. In the parallel treatment, psychosis and the substance abuse disorders are treated simultaneously but separately. It is mostly up to the user to follow and coordinate both of them. The integrated model of treatment provides that treatment for both the disorders is provided by the same team (Chow et al. 2013).

The sequential and parallel treatment have often been proven to be unable to meet users' needs, especially because the lack of coordination (Horsfall et al. 2009). Thus, patients may be referred from one service to another and users can be treated only for one of their two disorders. They may also receive incompatible or inconsistent and fragmented treatment. It is also possible that, facing many difficulties and seeing their needs unmet, they give up both treatments (Drake et al. 2008).

The integrated model is designed to reduce the gap between mental health and substance misuse services (Chow et al. 2013). However, in many countries it is hard to be implemented because national health systems keep these services separate and unifying them would implicate complex political choices and administrative efforts (National Collaboratory Centre for Mental Health 2011; Kavanagh et al. 2002). Thus, manualized integrated treatment, with one team looking after both disorders, is difficult to be broadly implemented. Furthermore, evidence about the efficacy of integrated treatment models is inconclusive, partly because of several methodological issues of research on this topic (Cleary et al. 2008). However, many authors have observed that integrated treatment, although not harmful, might not be more effective than standard care (Chow et al. 2013; Cleary et al. 2008). Indeed, even if there is uncertainty about its effectiveness, it is reasonable to implement part of its philosophy to counteract daily practice problems. In fact, many obstacles due to the services' dichotomy can be managed establishing a strong synergy between them (National Collaboratory Centre for Mental Health 2011).

The aim of ensuring a good quality of care to dually diagnosed individuals should start with setting formal collaboration protocols between local services. For each patient with dual diagnosis, they should set out their respective responsibilities, first of all agreeing on which are patients' main needs and which service has to coordinate treatment interventions (Horsfall et al. 2009). In case of psychosis, the

British National Collaborating Centre for Mental Health states that coordination should be kept by psychiatric services, due to the complex care needs of psychosis. Second, services have to regularly communicate and share information, to reduce redundant interventions and to fill care gaps. Similar agreements and collaborations should be set with other services and institution involved in patient's life, such as assisted housing institutions or the judiciary system (National Collaboratory Centre for Mental Health 2011; Kavanagh et al. 2002).

Besides organizational aspects, an appropriate treatment strategy should take into account two further issues, i.e., the stage of patients' motivations and coexisting physical, social, and financial problems (Horsfall et al. 2009; Drake et al. 2004). People suffering from severe mental illnesses have commonly low motivation to change. This is partly due to low self-esteem, tolerance of frustration, and social skills. Positive, cognitive, and negative symptoms of psychosis and being in contact with a substance-promoting social context all are factors that may further limit motivation (Horsfall et al. 2009). It is important to consider the role that the substance consumption has in patients' life, keeping in mind that different substances can have a different functional meaning in patients' life (e.g., cocaine against depressed mood and cannabis to facilitate socialization), and to evaluate patients' opinions and emotions about their personal situation and the treatment course, given that motivation can be hampered by many factors, including social and financial problems (Alverson et al. 2000).

Though treatment interventions in dual diagnosis are the same used for substance misuse and severe mental disorders, it is paramount to coordinate the efforts and to tailor care programs according to patient's characteristics. Irrespective of which of the two disorders may have supposedly come first, they should be treated simultaneously as for people with a single disorder (Drake et al. 2004).

122.2.4.1 Pharmacological Treatment

Pharmacological treatment of dual diagnosis involves treatment for both psychosis and substance use disorders. However, it must be paid attention to the risk of pharmacokinetic and pharmacodynamic interactions. There is currently poor evidence to support one antipsychotic over another or first- versus second-generation antipsychotic when treating schizophrenia with comorbid harmful substance use, abuse, or dependence, in relation to superiority in either reducing substance use or improving psychiatric symptoms (Lingford-Hughes et al. 2012). Among atypical antipsychotics, clozapine seems to be the most effective, both on psychotic symptoms and substance consumption (Green 2006; San et al. 2007). Clozapine has proven to be effective for several categories of misused substances, including cigarette smoking, stimulants, alcohol, and cannabis (Coyle 2006; Noordsy and Green 2003).

Mood stabilizers can be useful in case of schizoaffective disorders. Valproate has been proven to be effective in comorbid alcohol use disorders, and carbamazepine in substance misuse disorders. The efficacy of lithium among other drugs is scarcely known (National Collaboratory Centre for Mental Health 2011).

Methadone is associated with some risk of interactions. It is metabolized by the CYP3A4 cytochrome, so inductors of this cytochrome, such as barbiturates,

carbamazepine, phenytoin, and rifampicin, may decrease its serum level, which may result in a withdrawal syndrome. Cannabinoids, grapefruit juice, SSRIs, and other drugs may inhibit this cytochrome, thus increasing methadone's serum levels (National Collaboratory Centre for Mental Health 2011). There is also risk of interaction with antiretroviral therapy for HIV infection. For a complete explanation of the risk of interactions between methadone and other drugs, as well as for other drugs, it can be useful to consult the summary of product characteristics (SPC).

Lastly, it is important to pay attention to prescribing anticholinergic for extrapyramidal side effects and benzodiazepine, as they can be abused for their stimulating and sedative effect, respectively (Noordsy and Green 2003).

122.2.4.2 Psychological and Psychosocial Interventions

It is difficult to state which types of psychological and psychosocial interventions are more effective for comorbid substance use and psychotic disorders (Chow et al. 2013). Patients' stage of motivation is fundamental to tailor the intervention (Drake et al. 2004). A rationale framework for treatment includes several phases, i.e., engagement, motivation, active treatment, and relapse prevention (Horsfall et al. 2009; Drake et al. 2004). Engagement means establishing a trustful relationship between the clinician and clients. In this phase it is important to pay attention to the social and cultural background of users and to work for their gradual involvement, being flexible in interacting with them. Outreach interventions can be useful in this phase (Drake et al. 2004). About motivation to treatment, motivational interviewing is considered essential, especially in the early stages of treatment, to explore and try to modify the actual availability of clients to be engaged in treatment. For active treatment, many interventions are available. Among them, group approaches, mainly developed from cognitive-behavioral therapy, have proven to be useful across several types of populations, maybe depending on nonspecific factors such as education, skill building, and peer support (Horsfall et al. 2009). However, not all group interventions may be suitable for people with psychosis. For instance, 12-step programs for SUDs may be unhelpful, as this approach requires some introspection and talking about several intimate aspects of one's life. Therefore, adherence among people suffering from psychotic disorders could be hampered by their limitations in emotional expression and low social skills (Horsfall et al. 2009). Also residential treatment may be useful for dually diagnosed people, as it has proven to be effective for dual diagnosis clients who have failed outpatient programs (National Collaboratory Centre for Mental Health 2011). In terms of relapse prevention, one of the most effective interventions is contingency management, namely, setting rules about facilities and penalties depending on treatment compliance and substance consumption (Horsfall et al. 2009).

122.2.4.3 Admission to Psychiatric Wards

People with comorbid psychotic illness and SUDs have more frequent hospital admissions and use of emergency services. It happens quite frequently that they need to be admitted to a hospital ward, often a psychiatric one, for a psychotic relapse or for an intoxication syndrome (Morojele et al. 2012; Palomo et al. 2007).

However, they could be difficult to be managed due to their substance, alcohol, or drug craving or trafficking, violent or manipulative behavior, inappropriate relationship with other inpatients. However, psychiatric and substance misuse services, being a sort of safe and nonjudgmental environment, can become a favorable setting for substance consumption and dealing and related issues (Alverson et al. 2001). Therefore, it is important that some rules are set about their hospitalization, especially regarding visit arrangements, search procedures, and other security issues. Drug tests should be part of the routine. The aim is to have an environment free from drugs and alcohol, and these procedures should be explained to patients and their families. Treatments proven to be effective in outpatient settings are to be continued during the admission (National Collaboratory Centre for Mental Health 2011).

122.2.4.4 Prognostic Factors and Course

Dually diagnosed patients usually make slower progresses and have higher dropout rates (Horsfall et al. 2009). To deliver an effective treatment, it is important to frequently monitor patients' stages of motivation and to monitor retention in treatment, as this is directly related to psychosocial outcomes (Horsfall et al. 2009; Alverson et al. 2000).

Factors that may affect outcomes include dissatisfaction for quality of life, peer pressure, and lack of an alternative daily occupation or of satisfying social network once abstinence is attained, all of these can make patients relapse into consumption (Alverson et al. 2000). Positive prognostic factors include availability of a regular and interesting activity (other than substance consumption); a decent housing; a loving, caring relationship with someone sober and sensible about patient's mental illness; and a positive relationship with a mental health professional. Negative prognostic factors are related to patient's history, especially having experienced dire poverty, violence, or abuse and being grown up with someone in the family or in the household affected by a substance use disorder or a severe mental illness (Alverson et al. 2000).

Treatment of dual diagnosis challenges what we know about treatment of both substance use disorders and psychosis. It needs great efforts and even greater flexibility. Nonetheless, treatment needs of the comorbid population need to be met in order to guarantee a subjective quality of life at least as high as that of their nondependent counterparts.

122.3 Conclusion

The aim of this chapter was to give a brief overview of the epidemiological relevance, the main clinical features, and the treatment options of the comorbidity of psychotic disorders and substance use disorders. However, a large proportion of the etiology and physiopathology of these two syndromes is still unknown, and recent progresses in the knowledge of their neurobiology have a scarce impact on clinical practice.

Actually, the cornerstone of dual diagnosis treatment seems to be the coordination in the treatment of psychosis and substances consumption. A bulk of evidence

has shown that this strategy is peculiar for the efficacy of various treatment options, with great relevance both at health delivery and at individual level. An effective coordination should be achieved, first of all, in physicians' and other carers' minds.

Besides the need of coordinated treatment, it is important that every person involved in the care of dually diagnosed individuals understands the role of substance consumption in patients' life, as treatment should be tailored to give patients the opportunity to conceive and live a reliable alternative to drug abuse.

However, the need for further knowledge in this field cannot be quenched. Evidence about treatment outcomes in substance consumption is still scarce and partly contradictory, mainly because of methodological issues and, probably, because of the effect of undetected confounders.

Therefore, the comorbidity of psychosis and substance use disorders is a largely unexplored field, in which the clinical practice greatly relies on experience, flexibility, and common sense, but such a situation must be an even stronger trigger to the development of methodologically reliable scientific evidence.

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Attention Deficit/Hyperactivity Disorder and Substance Abuse

123

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Contents

Abstract

Although attention-deficit hyperactivity disorder (ADHD) has been increasingly diagnosed and treated in adult populations, adult ADHD in substance-dependent populations remains under-recognized. Converging data from epidemiologic and clinical samples show that adult ADHD is overrepresented among individuals with substance use disorders. This chapter provides information regarding the potential causes for this overrepresentation and factors that might lead to both under and overdiagnosis in individuals with substance use disorders, with attention paid to DSM-V criteria. While stimulants are considered a first-line treatment for adults with ADHD, it is less clear what the first-line pharmacologic or psychotherapeutic treatment approaches should be for adults with ADHD and

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co-occurring substance use disorders. Data collected from several clinical trials suggest that under closely monitored conditions, stimulants can be used safely to treat co-occurring ADHD and substance use disorders. However, the findings are mixed regarding the efficacy of both nonstimulants and stimulants in treating ADHD in this comorbid population. Taken together, the available published studies do provide some guidance on how to best approach this patient population. Future avenues of research are discussed.

123.1 Introduction

ADHD is a developmental disorder characterized by inattention, hyperactivity, and impulsivity such that there is significant impairment in functioning (DSM-5 2013). It has been increasingly recognized that many children continue to have impairing symptoms into adolescence and adulthood warranting clinical attention. ADHD is highly inheritable and although it is relatively common in adults, it often goes undiagnosed and untreated (Kessler et al. 2006; Smith et al. 2009). Some of the potential reasons include (1) practicing adult psychiatrists and psychologists may not have been trained to recognize this condition, (2) patients present with other psychiatric conditions that become the focus of clinical attention, (3) the condition is not viewed as a major clinical concern, (4) the psychiatric symptoms associated with ADHD are incorrectly explained by other conditions (e.g., bipolar disorder, active substance use disorder).

Clearly, there is substantial morbidity associated with ADHD. Compared to those with ADHD, adults with ADHD have greater legal difficulties, motor vehicle accidents, higher divorce rates, increased workplace costs, and poorer life satisfaction (Jerome et al. 2006; Kessler et al. 2009; Mannuzza and Klein 2000; Wu et al. 2007). In a large adult population in an employer-sponsored health plan, patients with ADHD incurred substantially higher total annual health-care expenditures than those without ADHD (44,306 vs. $2,418; Hodgkins et al. 2011). Longitudinal studies have demonstrated that adults diagnosed with ADHD in childhood have lower-ranking occupational positions and formal schooling as adults (Mannuzza et al. 1997). Impulsive/hyperactive symptoms in childhood are associated with greater risk of early onset of substance use (Chang et al. 2012), abuse, and dependence in adolescence and adulthood (Elkins et al. 2007). Moreover, persistence of symptoms may increase the likelihood of substance dependence into adulthood, notably for both men and young women (Biederman et al. 2010; Mannuzza et al. 1993).

Recognizing the link between ADHD and substance abuse is relevant to clinicians in that substance abusers with ADHD who enter addiction treatment have been shown to have worse outcome than those without ADHD, despite more treatment exposure (Carroll and Rounsaville 1993; Levin et al. 2004; Wilens et al. 1998). Further, substance abusers with ADHD entering treatment have higher rates of other psychiatric comorbidity (e.g., depression) that may worsen treatment success unless these additional comorbidities are simultaneously addressed (Clure et al. 1999; Levin et al. 1998; Wilens et al. 1998). While there is increasing

evidence that ADHD is associated with increased rates of substance abuse (and vice versa), there remains modest empirical evidence regarding how to best treat this patient population.

This chapter will present epidemiologic data supporting the link between these disorders, possible etiologies to explain this link, some of the complicating issues associated with screening and diagnosing adult ADHD among those with and without substance use disorders, treatment options for this comorbid group, and the controversies that exist in treating active substance abusers with ADHD.

123.2 ADHD Features

123.2.1 Epidemiology

ADHD is a common childhood disorder with prevalence rates in the United States ranging from 5 % to 10 %. While it is estimated that up to 60 % of children continue to have impairing symptoms into adulthood, the minority continue to meet full DSM-IV criteria into adulthood (Biederman et al. 2000; Fayyad et al. 2007; Kessler et al. 2005; Mannuzza et al. 1993; Rasmussen and Gillberg 2000). While the prevalence rate commonly given for adult ADHD is 4.4 % (Kessler et al. 2006), a recent meta-analysis of six prevalence studies has found that this rate may be closer to 2.5 %. Regardless of the exact rate, the significant association of ADHD and substance use disorders is becoming increasingly clear. Specifically, data from the National Comorbidity Survey Replication Study (NCS-R) has found that adults with ADHD have higher rates of having a substance use disorder (SUD) than those without ADHD (15.2 % vs. 5.6 %). Similarly, individuals with SUD are more likely to have ADHD than those without an SUD (10.8 % vs. 3.8 %).

In clinical substance abuse treatment settings, this association may be more pronounced. In a meta-analysis, Oortmerssen et al. (2012) found that the overall rate of adult ADHD was 23.1 % (CI: 19.4–27.2 %), somewhat higher than the rates of ADHD observed in nonclinical samples. This disparity is likely explained by Berkson's bias (1946) which is the phenomenon that patients evaluated in clinical settings are more likely to have comorbid conditions. Individuals who are experiencing more psychological distress and the consequences of having multiple comorbidities are more likely to seek out treatment. Perhaps somewhat surprising from this meta-analysis was the finding that the rate of ADHD was lower in cocaine-dependent individuals compared to other drug-abusing groups. Based on the self-medication hypothesis, it might be expected that those with ADHD would more commonly seek out stimulants, such as cocaine, to ameliorate their ADHD symptoms rather than alcohol or other illicit drugs (Khantzian 1983, 1985). However, this finding does not necessarily negate this hypothesis. Individuals with ADHD may seek out chemical solutions that are readily attainable (such as nicotine, marijuana, or alcohol) and are perceived to lessen undiagnosed ADHD symptoms or associated dysphoria or anxiety.

Substance abusers with ADHD frequently have additional psychiatric disorders which further complicate the diagnosis and treatment of the ADHD. In the NCS

Replication, adults with ADHD were more likely to have major depression (OR = 2.7), dysthymia (OR = 7.5), bipolar disorder (OR = 7.4), or an anxiety disorder (OR = 3.7). Alternatively, for those with mood disorders or anxiety disorders, adult ADHD is overrepresented (2.9 and 2.8, respectively). Multiple comorbidities among those with ADHD have been observed in clinical samples of substance abusers (King et al. 1999; Levin et al. 1998). Moreover, Wilens et al. (2005) have found that the presence of ADHD and an additional substance use disorder significantly increases the risk of conduct disorder, a mood disorder, or an anxiety disorder. This is clinically relevant in the presence of these other Axis I conditions, the treatment of ADHD may be viewed as less important and not warrant clinical intervention (Kessler et al. 2006). In a review of the literature, Kooij et al. (2012) outline the main comorbid disorders associated with ADHD. These include (1) mood disorders, (2) substance use disorder, (3) impulse control disorders, (4) anxiety disorders, (5) sleep disorders, and (6) learning disabilities. While it is beyond the scope of this chapter to discuss these additional comorbidities, it is incumbent on the clinician to assess for these conditions or provide appropriate referral (i.e., to learning or sleep specialists) if necessary.

Recently, there has been increased recognition of the overlap of obesity and eating disorders (primarily bulimia, binge eating) among those with ADHD (Mikami et al. 2008; Pagoto et al. 2009). Notably, the impulsive symptoms associated with ADHD may be "driving" the eating disordered behavior rather than the inattentive symptoms. Impulsivity has been shown to predict problematic substance use and perhaps not surprisingly there has been a greater awareness of the neurobiologic and behavioral commonalities of obesity and substance use disorders (Acosta et al. 2008; Volkow et al. 2010). Similar to other comorbid conditions, the initial priority in treatment might be the condition or conditions warranting immediate clinical attention, but attention to multiple conditions simultaneously might be preferable when possible.

123.2.2 Etiology

The development of ADHD is influenced by multiple genes, non-inherited factors, and their interaction (Thapar et al. 2007). There is no single genetic or environmental cause of ADHD and the presence of risk factors does necessarily result in the development of the disorder. Chance events, such as non-inherited spontaneous genetic changes, may play a role. The population of individuals with ADHD are heterogeneous with regard to genetic risk factors and exposure to environmental risks. Genes may alter the sensitivity to environmental risks and inherited factors can also influence the probability to exposure to certain environmental risks, making distinctions between genetic and environmental risks difficult. While the evidence is strong that there is an inherited contribution to ADHD, how exactly that risk is passed on is unclear. Likewise, while there is evidence that environmental risk factors are important independent and modifiers of ADHD risk, which environmental risk factors are most important and how the mechanism by which they exert their influence on the development of ADHD is unclear.

First-degree relatives of those with ADHD are two to eight times more likely than the general population to develop ADHD (Faraone et al. 2005). Mean heritability estimates are approximately 79 % (Lichtenstein et al. 2010). High heritability estimates include the effect of genetic inheritance, but likely also shared environmental influences between parents and their children. The most robust evidence of association with ADHD has been the DRD4 variant of the D4 receptor gene (Gizer et al. 2009), which binds both dopamine and norepinephrine. Another dopamine receptor gene, DRD5, has also been associated with the risk of developing ADHD (Gizer et al. 2009). The dopamine transporter gene (DAT1) has been associated with the risk of ADHD and to interact with environmental factors such as maternal alcohol (Brookes et al. 2006) and cigarette use (Becker et al. 2008). The catechol-O-methyl transferase (COMT), which degrades dopamine, has been associated with conduct disorder in ADHD (Langley et al. 2010), but not antisocial behavior alone (Caspi et al. 2008), suggesting a specific role COMT variants in modifying ADHD.

There are a number of environmental risk factors associated with ADHD, including alcohol (Linnet et al. 2003), cigarette (Langley et al. 2005), and other substance use during pregnancy, but it is not known if these associations are causal or simply markers for other environmental risk factors not yet determined. Environmental toxins, such as lead (Nigg 2008) and polychlorinated biphenyls (PCBs) (Sagiv et al. 2010), have been studied as potential risk factors for ADHD with inconclusive results, as these toxins produce cognitive impairment that may mimic, rather than cause, ADHD.

Despite extensive research over the recent decades, the causes of ADHD remain largely unknown, even less is known about risk factors, other than treatment, that may modify outcome. There are no reliable biomarkers for ADHD and no prenatal genetic testing. Like all complex disorders, ADHD is not explained by any single risk factor alone and not all of those exposed to a given risk show the disorder. For clinicians, the most useful tool remains taking a careful family history, which might reveal diagnosed or undiagnosed cases of ADHD.

123.2.3 Diagnosis

For DSM-5 the adolescent adult diagnosis requires five or more of the nine symptoms of inattention and/or five or more of the nine symptoms of hyperactivity-impulsivity, whereas children are required to have six inattentive or six hyperactive-impulsive symptoms. The additional four criteria require (1) several symptoms prior to the age of 12; (2) several impairing symptoms in at least two settings; (3) clear evidence of the symptoms that interfere or reduce the quality in social, academic, or occupational functioning; and (4) symptoms that do not occur only during the course of schizophrenia or another psychotic disorder or are better explained by another mental disorder. Individuals may have one of the three subtypes: (1) predominantly inattentive, (2) predominantly hyperactive-impulsive, or (3) combined presentation (i.e., the individual meet five out of 9 symptoms of hyperactivity-impulsivity and five out of 9 symptoms of inattention).

Importantly, an adult cannot be diagnosed with ADHD if he/she did not have ADHD symptoms as a child. However, a full symptom count is not necessary. Importantly, ADHD cannot "come and go." If an individual met the criteria for ADHD but for the past 6 months dues not meet full criteria, then they are considered to be in partial remission if there remains clear impairment. If an individual never met full criteria, then they can be either diagnosed with other specified ADHD (if a reason is given by the clinician, such as never had adequate number of inattentive or hyperactive-impulsive symptoms) or unspecified ADHD (if no specific reason is given). However, for both diagnostic categories the ADHD symptoms have to produce significant distress or clear impairment in social, occupational, or other areas of functioning. These two diagnostic categories provide substantial leeway for clinicians to make an ADHD diagnosis. It remains unclear what percentage of clinicians would medically treat individuals who do not meet full diagnostic criteria but meet diagnostic criteria for these two latter categories.

123.2.3.1 Issues Complicating Adult ADHD Diagnosing with Special Focus on Substance Abusers

Several issues that are problematic when assessing individuals for ADHD include (1) the developmental appropriateness of the symptoms, (2) the age criterion, (3) determining what defines other specified or unspecified ADHD, (4) additional psychopathology, and (5) secondary gain. These issues are further complicated by the presence of a past or ongoing substance abuse problem. Because ADHD was initially viewed as a childhood disorder that adults "outgrew," some of the core symptoms of ADHD tend to be child specific. Certain symptoms, such as "can't stay seated," runs/climbs excessively, or "can't play/work quietly," are not easily endorsed by adults. Unless the interviewer is experienced in diagnosing ADHD and makes these symptoms more adult relevant, then it is likely that ADHD will be underdiagnosed. This has been somewhat mitigated in that unlike DSM-IV, DSM-5 now includes examples of these symptoms that are more adult relevant. For example, adults may report that they choose very active jobs rather than report that they "can't sit still." Further, an adult may not report that they "squirm" or "fidget" or "driven by a motor" but rather they are more likely to report being a "workaholic" or feel overwhelmed or overscheduled.

The age criterion has been modified by DSM-5. In DSM-IV, the full diagnosis of ADHD requires that impairing symptoms occur prior to the age of 7. For DSM-5, some symptoms need to be present prior to the age of 12. However, even with raising the age criterion, some patients might have difficulties with childhood recall. Similarly, parents or older family members may not recall elementary school behaviors. Report cards can sometimes pinpoint when the impairing symptoms began or if there were behavioral problems in early school grades. For substance abusers who may have estranged relationships with their parents, corroborative information may be particularly difficult to attain.

Expert clinicians such as Barkley and Biederman (1997) questioned the validity of the age criterion and growing evidence supported this (Faraone et al. 2006). Specifically, Faraone et al. (2006) found that adults with late-onset ADHD

(symptoms that began after the age of 7 but most commonly before the age of 12) had comparable psychiatric comorbidity, functional impairment, and familial transmission of ADHD as seen in those diagnosed with early onset ADHD, suggesting that there is concurrent validity of the late-onset variant with the full diagnosis. These data, along with others, supported the DSM-5 change in which the age criterion will be raised to under the age of 12. While some clinicians have probably been diagnosing adults with ADHD, even when the early onset of symptoms could not be determined, other clinicians may have not have diagnosed individuals if the age criterion was not met. The possible impact is that the relaxed criterion will lead to higher rates of detection, particularly among adult substance abusers, who may have cognitive difficulties due to alcohol or drug use recalling symptoms prior to the age of 7 (Bates et al. 2002; Pope et al. 2003).

The new diagnostic categories, other specified and unspecified ADHD (which replace the DSM-IV ADHD.NOS diagnosis), may also lead to some consternation. While clinicians can arrive at this diagnosis through various routes, perhaps the most common one is when an individual meets the full adult criteria except for the age criterion. However, other possibilities include meeting less than five inattentive or hyperactive/impulsive criteria adulthood. It remains a question of clinical judgment of whether three or four symptoms of inattention or hyperactivity-impulsivity should be present in adulthood to meet a clinical diagnosis of other specified ADHD. At present, if an adult had childhood or adolescent ADHD and currently has less than five symptoms in adulthood, then based on current DSM-IV criteria, the individual would be considered to be in partial remission. Further, what is not clear with the DSM-5 (and DSM-IV) criteria is what an adequate number of childhood symptoms is. At present, "several" symptoms in childhood are necessary to meet an adult diagnosis, rather than the full symptom count which is required when diagnosing a child. Also, in contrast to DSM-IV in which childhood symptoms had to be impairing, the symptoms only need to be present in DSM-5. It remains to be seen whether these changes will result in better identification of adult ADHD or overdiagnosis.

Kooij et al. (2012) noted that although pharmacotherapy is effective for adolescents and young adults with ADHD, prescribing by physicians of patients with ADHD drops substantially from age 15 to 21, with this decrease greater than the age-related decline in symptoms. To some degree this might be due to the incorrect assumption that fewer symptoms are associated with less severity and reduced need for medications. For substance abusers, the diagnosis may be complicated in that acute use or withdrawal from alcohol or other substances may "mimic" ADHD and lead to overdiagnosis. When used chronically, alcohol, marijuana, nicotine, and cocaine can produce restlessness and agitation during withdrawal (Grahman et al. 2003; Miller and Gold 1998). Both nicotine and cocaine withdrawal have been associated with concentration difficulties.

As mentioned previously, numerous psychiatric disorders are overrepresented among those with ADHD. The presence of these additional conditions can lead to both overdiagnosis. If the clinician incorrectly assumes that the observed ADHD symptoms are better accounted for by another psychiatric disorder, then the ADHD

may go undiagnosed. Alternatively, if there are psychiatric symptoms that are better explained by another disorder but attributed to ADHD, then this will lead to overdiagnosis. In many cases, it is not entirely clear unless the patient is monitored over time. From a practical perspective, when there is some diagnostic confusion, the clinician makes his/her best education guess and treats the condition warranting clinical attention. However, in many instances there might be ADHD along with depression and/or anxiety requiring more complicated therapeutic regimens. Not surprisingly, the addition of a substance use disorder further complicates the diagnostic assessment. For example, both hypomania and ADHD share excessive talkativeness, restlessness, racing thoughts, impulsive behaviors, difficulty with concentration, decreased attention and distractibility, and mood swings/anger outbursts. Not surprisingly, because of the numerous overlap in symptoms, distinguishing whether an adult has ADHD, hypomania, or both conditions can be quite difficult. This can be mitigated by the presence of fluctuating episodic mood swings or psychosis, symptoms not associated with ADHD alone.

Notably, ADHD is often underdiagnosed in substance abuse treatment settings not because of difficulties distinguishing ADHD from other conditions but rather because of the lack of awareness or training in diagnosing ADHD. These patients may attribute their impatience, restlessness, or procrastination to being "hot-headed," "easily bored," or "lazy." Further, many of the consequences of ADHD (such as work failure and poor educational attainment) also are associated with substance use disorders (Kalbag and Levin 2005).

While underdiagnosis is common, there are several reasons why adolescents and adults might "feign" ADHD symptoms, leading to overdiagnosis. Because it is a clinical diagnosis, it is possible for individuals to endorse ADHD symptoms and meet criteria for ADHD, even when they do not suffer from the disorder. Being diagnosed with ADHD might allow increased time for test taking or special accommodations in the classroom. Athletes, both nonprofessionals and professionals, might report having ADHD symptoms in order to obtain stimulants, with the hope of improving their performance. Similarly, high school and college students may report having ADHD symptoms to enhance their academic performance or combat fatigue when they need to stay awake to study for finals or finish coursework. Moreover, some individuals, particularly those with underlying substance use disorders, may feign ADHD symptoms in order to procure a stimulant prescription to get high.

Another reason for overdiagnosis is mistakenly assuming that inattentive or hyperactive symptoms are due to ADHD rather than medical conditions such as sleep apnea, anemia, and thyroid problems (Kooij et al. 2012; Murphy and Gordon 2006). Finally, inadequate consideration to the impairment criterion may lead to overdiagnosis. There are many times when individuals can be inattentive or impulsive and demonstrate many of the symptoms associated with ADHD. However, individuals with ADHD have substantial impairment from these symptoms. Examples of impairment are critical to obtain during the comprehensive interview. For substance abusers this may be difficult since impairment may be due to the addictive behavior rather than the ADHD symptoms.

Moreover, for active substance abusers, the diagnosis may be complicated in that acute use or withdrawal from alcohol or other substances may "mimic" ADHD and lead to overdiagnosis. When used chronically, alcohol, marijuana, nicotine, and cocaine can produce restlessness and agitation during withdrawal (Grahman et al. 2003; Miller and Gold 1998). Both nicotine and cocaine withdrawal have been associated with concentration difficulties. Preferably, if a period of abstinence can be attained, it may help tease out ADHD symptoms from those that are substance induced.

There are several diagnostic instruments that have been modified for use in adults or have been specifically designed for adults to attain an adult ADHD diagnosis. These include the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiological Version (Kiddie SADS-E; Orvaschel 1985); the Structured Clinical Interview for DSM-IV, Childhood Version (KID-SCID; Hien et al. 2001); the Adult ADHD Clinical Diagnostic Scale (ACDS) V1.2 (Adler et al. unpublished instrument); and the Conners' Adult ADHD Diagnostic Interview for the DSM-IV (CAADID; Epstein et al. 2001). These instruments attempt to improve diagnostic accuracy by including adult symptoms that are developmentally appropriate and provide a structured approach ensuring that all of the ADHD criteria are met. While these instruments have good face validity, their reliability has not been evaluated in active substance abusers.

123.2.4 Screening for ADHD

Although the diagnosis of ADHD requires a comprehensive clinical assessment, screening instruments can prove useful in identifying those who might have ADHD. Commonly used instruments include the Brown Attention-Deficit Disorder Rating Scale for Adults (Brown 1996), the Wender Utah Rating Scale (WURS; Ward et al. 1993), the Conners' Adult ADHD Rating Scales (CAARS; Conners et al. 1999), the ASRS-v1.1 (Adler et al. 2006), the ADHD Rating Scale (Murphy and Barkley 1996), and the Attention-Deficit Scales for Adults (ADSA; West et al. 2003). The Brown scale has good psychometric properties but does not include questions about hyperactive symptoms. The WURS is often used for screening adults for childhood ADHD symptoms and is based on Wender Utah Criteria for ADD (Wender et al. 1985). The CAARS has the advantage of allowing for self-report and observer report and is available in screening, short, and long versions. These scales include core DSM-IV symptoms but also associated ADHD symptoms such as mood dysregulation and low self-esteem. The ADSA is one of the few instruments that have been evaluated in substance-abusing populations and found to have clinical utility in identifying ADHD (West et al. 2003). The Adult Self-Report Scale (ASRS; 18) has the convenience of being short (six items) and has reasonable psychometric properties. The ADHD Rating Scale – IV (Murphy and Barkley 1996) incorporates the 18 ADHD symptoms and requires the individual to self-rate the frequency/severity of symptoms.

Until recently, most of these instruments have not been tested in substance-abusing populations. Using the ASRS-V1.1, Daigre et al. (2009) found that it had

good sensitivity (87.5 %) in a substance-abusing population. As mentioned above, the ADSA has also been evaluated in active substance abusers and was found to have fairly good sensitivity (0.71) and specificity (0.82). The ASRS-V1.1 is substantially shorter than the ADSA (6 vs. 54 items), suggesting it might have greater utility in busy, clinical settings. Recently, a study was conducted to assess the clinical utility of three of the short, commonly administered instruments (e.g., the WURS, Adult ADHD Rating Scale, and the ASRS-V1.1) in treatment-seeking cocaine abusers (Dakwar et al. 2012). The psychometric properties of the instruments were tested by comparing the sensitivity, specificity, and positive and negative predictive values of these instruments with the Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID; Epstein et al. 2001) serving as the "gold standard." All three instruments demonstrated adequate sensitivity, specificity, and positive/negative predictive values, with the WURS having the greatest sensitivity and the Adult ADHD Rating Scale performing best on predictive parameters. While these findings suggest that standard ADHD instruments may be reasonably applied to screen for ADHD in active substance abusers, the studies conducted to date have been rather small and did not control for acute intoxication or withdrawal.

Another screening approach that might be considered is to use neurocognitive testing or other physiologic findings to identify those with ADHD. While there are numerous neuropsychological tests, neuroimaging findings, and electrophysiologic data that have found differences between those with and without ADHD, none of these tests have adequate positive predictive value (i.e., if the result is positive, then the individual has the disorder) to be used as a cost-effective method to accurately identify those with ADHD. To date, continuous performance tasks have demonstrated the most reasonable sensitivity and specificity (Gordon et al. 2006), but cannot be used to make an ADHD diagnosis. Moreover, while some practitioners include neurocognitive tests as part of their ADHD assessment, it is not required or necessary in order to make an ADHD diagnosis. Given that chronic alcohol and drug abuse has been shown to alter cognitive functioning, it remains dubious to use these tests to screen substance abusers for ADHD. However, this does not negate the clinical utility of these approaches to better understand the pathophysiology of ADHD and/or substance abuse and the potential remediable areas of cognitive deficits that an individual patient may have as a result of his/her ADHD.

123.2.5 Abuse Potential and Misuse of ADHD Medications

Prescription amphetamine misuse peaked in the last 1990s but still remains a problem warranting attention. With the substantial increase in stimulant prescriptions, misuse and diversion of medication for nonmedical purposes have become a considerable clinical concern, particularly on college campuses. Wilens et al. (2008) define misuse and diversion of ADHD medications in the following manner:

> Misuse includes taking ADHD prescriptions not prescribed to the individual or talking medication differently than they were prescribed (e.g., more than prescribed, taking alcohol or other drugs). Diversion of stimulants is the transfer of ADHD prescription medications from one individual who does have a prescription to another individual who does not have a prescription. This transfer includes the selling, trading, or giving away prescription medication.

While some surveys include concurrent use of alcohol or drugs with appropriately prescribed stimulants for AHD as "misuse," other surveys do not. This can lead to wide variability in misuse rates. Further, differences in sample attainment and manner in which questions are asked can also lead to variability in rates of misuse. Nonetheless, surveys do provide an indication of how widespread prescription stimulant misuse and diversion occurs. The 2010 National Survey on Drug Use and Health, a large epidemiologic survey conducted in the United States, found that 0.4 % of Americans aged 12 years or older reported current (last 30 days) nonmedical use of prescription stimulant medications (2010). While these rates are substantially lower than current nonmedical use of pain relievers or tranquilizers (2 % and 0.9 %, respectively), the risks of prescribing stimulant medications in a population vulnerable to misuse and abuse must be considered carefully (i.e., college students abusing alcohol or other drugs).

In a comprehensive review of 21 studies representing over 113,000 subjects, the rates of past year nonprescribed stimulant use ranged from 5 % to 9 % in grade school- and high school-age children and 5–35 % in college-age individuals (Wilens et al. 2008). In a large random survey of undergraduates at a large public American university, 54 % of student misusing stimulants reported using stimulants to concentrate, 43 % for alertness, and 43 % to get high (Teter et al. 2005). This is not simply a problem in the United States. In a survey with 307 fraternity members in the United Kingdom, 55 % reported nonmedical use of stimulants. The reasons given for stimulant misuse included the following: to stay awake (74 %), to concentrate on work (59 %), to help memorize (30 %), and to stay awake and have fun (17 %). Perhaps most concerning was that 90 % reported stimulants were "easy" or "very easy" to obtain and 89 % thought stimulants were "not dangerous at all" or "slightly dangerous."

Notably, those who use stimulants are more likely to use nicotine, alcohol, or other drugs (Wilens et al. 2006). Further, most misuse of stimulants was by oral administration, although intranasal use has been commonly reported (White et al. 2006). Repeatedly, surveys have found that the vast majority of misused stimulants are immediate preparation rather than extended-release preparation (Bright et al. 2007; Kroutil et al. 2006; Wilens et al. 2006). In an adult sample prescribed stimulants for their ADHD, most with substance abuse histories, misuse of IR preparation occurred substantially more frequently than those using ER preparations alone or both IRB and ER preparations (81 % vs. 16 % and 3 %, respectively).

Importantly, numerous surveys that document high rates of misuse often do not adequately address the motivation or context of the "misuse." For example, while some studies report that a substantial minority of individuals who are prescribed stimulants for their ADHD misuse their medications (Jardin et al. 2011), until recently, the reasons for misuse have not been adequately explored.

Two surveys conducted among US college students prescribed stimulants for their ADHD found that misuse was more common among those that used alcohol and other drugs (Jardin et al. 2011; Rabiner et al. 2009). While it is somewhat reassuring that most students used their ADHD medications as prescribed, misuse and diversion were not infrequent (Rabiner et al. 2009). However, the primary motives for misuse were to concentrate better while studying, to be able to study longer, to feel less restless while studying, and to concentrate better in class. Much less common reasons included to get high or to counteract the effects of other drugs. Rabiner and colleagues posit that undergraduates with ADHD might not perceive their treatment to be adequate and may be "underdosed." It remains unclear whether the prescriptions written for college students meet their needs for symptom coverage required into the early morning hours for studying or finishing papers.

For some students who misuse stimulants but are not prescribed stimulants for ADHD, expert clinicians have speculated that some of these adolescents and young adults may be self-medicating undiagnosed ADHD (Rostain and Ramsay 2006; Upadhyaya et al. 2005). Upadhyaya et al. (2005) found that a substantial group of college students who misuse stimulants had ADHD symptoms, although they were not diagnosed with ADHD. While it may seem that stimulant use to fight fatigue in college or to self-medicate undiagnosed or untreated ADHD might be of lesser clinical concern than stimulant use to "get high," this is still worrisome because repeated stimulant use that is not medically monitored might lead to problematic use. Further, there may be underlying cardiac problems or an untreated psychiatric illness (e.g., bipolar disorder) that might be exacerbated by stimulant use.

As noted above, several surveys suggest that long-acting preparations have less abuse potential. There are several explanations for this. Many of the long-acting preparations are difficult to crush and thereby enhance absorption. While immediate-release methylphenidate can be crushed and snorted or dissolved in water and injected, this is not possible with various formulations such as the osmotic release oral system (OROS) methylphenidate or lisdexamfetamine (LDX). OROS-methylphenidate (Concerta) uses an osmotic delivery system in which the tablet is coated with immediate-release methylphenidate for initial dosing, and the long-acting component is delivered by an osmotic pump that slowly releases methylphenidate (Daughton and Kratochvil 2009). LDX, a prodrug, is a therapeutically inactive molecule until it is converted to l-lysine and active d-amphetamine and is associated with a longer duration of effect and reduced abuse potential (Jasinski and Krishnan 2009). Volkow et al. have shown that drug liking is associated with the rapid rise of plasma stimulant levels and brain concentration (Parasrampuria et al. 2007; Volkow et al. 1995). Therefore, it is not surprising that there is less diversion with long-acting formulations, with slower onset of action and lower peak plasma levels, than immediate-release preparations.

Under controlled conditions, the lower abuse potential of long-acting preparations has been confirmed in adults without substance abuse histories, those with histories of drug abuse, and active substance abusers. Kollins et al. (1998) found that healthy adult controls were more likely to report "good drug effects" with short-acting methylphenidate compared to sustained-release methylphenidate. In a subsequent

study with healthy adult controls, therapeutic oral doses of IR-methylphenidate were compared to OROS-methylphenidate. Those who received IR-methylphenidate reported "liking the effect" more than those with receive OROS-methylphenidate (Spencer et al. 2006).

In a double-blind, placebo-controlled study in adults with drug abuse histories, low and high doses of IR- MPH (50 and 90 mg) and OROS-MPH (54 and 108 mg) were administered. While the lower and higher dose of IR-MPH produced greater subjective effects than placebo, only the higher dose of OROS-MPH produced greater subjective effects than placebo (Parasrampuria et al. 2007). Another study in adults with stimulant abuse histories and intravenous doses of LDX and IR-d-amphetamine was compared to placebo. IR-d-amphetamine, but not LDX, produced greater subjective effects than placebo (Jasinski and Krishnan 2009). When oral doses are administered, low doses of LDX (50 and 100 mg) did not produce greater subjective effects than placebo. However, the highest dose of LDX (150 mg) produced greater drug liking than placebo, suggesting that high doses might be more likely to be abused (Jasinski and Kovacevic-Ristanovic 2000).

Another formulation that has been tested for its abuse potential is the methylphenidate transdermal system (MTS; Daytrana). The MPH patch (Daytrana) contains a multipolymeric adhesive layer attached to a transparent backing. MPH is slowly released with peak levels achieved 7–9 h after the patch is applied (Daughton and Kratochvil 2009). In a small sample of stimulant abusers, a double-blind, crossover design was conducted in which the MPH patch was applied to an unheated or heated arm or to the buccal mucosa and compared to placebo as well as subcutaneous methylphenidate. Regardless of where the MTS was applied, MTS produced greater positive subjective effects than the placebo and was comparable to subcutaneous methylphenidate (Jasinski and Krishnan 2009). However, because MTS was not compared to an immediate-release methylphenidate preparation, it cannot be definitely determined whether the patch has less abuse potential than an IR-MPH formulation.

These finding suggests that long-acting stimulants are preferable for populations at risk for substance abuse, but positive subjective effects can be elicited by changing the route of administration or taking more than prescribed. To date, there are limited data assessing the safety or abuse potential of stimulants in substance abuse populations with ADHD. In a laboratory study in nontreatment-seeking cocaine abusers with ADHD, participants were maintained on low or high doses of sustained-release methylphenidate or placebo and were administered intravenous cocaine. Under controlled laboratory conditions, the combination of intravenous cocaine and sustained-release MPH did not produce any untoward events. The high dose MPH group produced less (rather than greater) subjective effects than placebo when cocaine was administered. Moreover, in a subsequent study in which participants were allowed to self-administer cocaine while maintained on low and high doses of MPH or placebo, those maintained on the high dose MPH were less likely to self-administer the high dose of cocaine compared to those maintained on placebo (Collins et al. 2006). This is notable because it suggests that the sustained-release MPH preparation does not enhance and perhaps reduces the likelihood of greater

cocaine use among cocaine abusers with ADHD. However, this small study did not compare the abuse potential of short- and long-acting formulations to nonstimulants that are used to treat ADHD.

There remains much consternation regarding whether or not to prescribe stimulants for active substance abusers with ADHD. While the Collins et al.'s (2006) study has obtained some reassuring data regarding the use of sustained-release MPH in active cocaine users, a comparison of subjective effects and self-administration of immediate- and long-acting stimulant formulations and nonstimulants used to treat ADHD (e.g., clonidine extended release, atomoxetine) in active substance abusers with ADHD has not been conducted.

Perhaps not surprisingly, atomoxetine has been repeatedly shown to have less abuse liability than stimulant preparations in healthy controls and occasional drug users (Heil et al. 2002; Lile et al. 2006) and in active stimulant abusers (Jasinski et al. 2008). While this might suggest that atomoxetine should be the first-line treatment, there are some limitations with its use. Compared to stimulants, atomoxetine may take several weeks before it adequately reduces ADHD symptoms, side effects often occur prior to noticeable clinical improvement, and it has not been shown to be as effective as stimulants in treating those with ADHD (Faraone and Glatt 2010).

123.2.6 Pharmacologic Treatments for ADHD

123.2.6.1 Stimulant Medications

Amphetamine analogs and methylphenidate are the stimulant medications and are first-line treatments for both children and adult ADHD in the United States. Methylphenidate is a piperidine derivative that is structurally related to amphetamine, whose mechanism of action is primarily due to dopamine and noradrenergic reuptake blockade in the striatum (Brunton et al. 2011). Amphetamine stimulates the cerebral cortex and the reticular activating system primarily by enhancing dopamine release, although it also blocks dopamine reuptake (Brunton et al. 2011). Both methylphenidate and amphetamine analogs are available in many immediate-release and extended-release preparations. Lisdexamfetamine, a prodrug, was FDA-approved initially for childhood ADHD and more recently for adult ADHD. Because it is a prodrug, it is a therapeutically inactive molecule until it is converted to l-lysine and active d-amphetamine and is associated with a longer duration of effect and reduced abuse potential. Side effects most commonly associated with amphetamine and methylphenidate administration include insomnia, emotional liability, nausea/vomiting, nervousness, palpitations, elevated blood pressure, and rapid heart rate. Rare but serious adverse effects include severe hypertension, seizures, psychosis, and myocardial infarction.

123.2.6.2 Nonstimulant Medications

Two nonstimulant medications have been approved for ADHD. Atomoxetine is FDA-approved for pediatric and adult use and guanfacine-extended release is

FDA-approved for pediatric use. All other nonstimulant medications, such as bupropion, desipramine, and modafinil, are "off-label" for ADHD and are generally considered second- or third-line treatments. Atomoxetine, a centrally acting noradrenergic reuptake inhibitor (Adler et al. 2005; Michelson et al. 2003), has the advantages of a lower abuse potential than stimulants, has long-lasting therapeutic effects, and is not a controlled substance. However, the initial therapeutic effects are gradual, sometimes taking 2–6 weeks to achieve therapeutic efficacy. This contrasts the onset of action of stimulants which can show clinical effects shortly after the first dose (Daughton and Kratochvil 2009). Common side effects of atomoxetine include sedation, appetite suppression, nausea, vomiting, and headache. Rare but serious side effects reported in children and adolescents include increased suicidal ideation and hepatotoxicity. While clinically effective, in a meta-analysis, atomoxetine had a medium effect size compared to large effect sizes for immediate-release and sustained-release stimulants (Faraone and Glatt 2010).

Guanfacine-extended release, an alpha-2 agonist, has been shown to be nearly as effective as stimulants in youth (Faraone and Glatt 2010), and although it has not been as extensively studied in adults, guanfacine appears efficacious for adult ADHD symptoms (Taylor and Russo 2001). Commonly, guanfacine is used adjunctively with stimulants to further reduce ADHD symptoms among those that have had a partial response to stimulants (Spencer et al. 2009). Common side effects of guanfacine include somnolence, headaches, sedation, and blood pressure decreases (Connor et al. 2012; Sallee et al. 2009). ADHD improvements have been observed after 1 week of medication administration and may be particularly useful for those with comorbid sleep and tic disorders (Sallee et al. 2009; Wolraich et al. 2005).

Several antidepressants, such as desipramine, bupropion, and venlafaxine, have been evaluated for ADHD, and while they have some efficacy in reducing ADHD symptoms, they are less effective than stimulant medications (Wolraich et al. 2005). Bupropion has been well studied and has shown efficacy for both children and adults with ADHD, albeit less so than stimulant medications (Daughton and Kratochvil 2009; Faraone and Glatt 2010). Common side effects include irritability and insomnia. Drug-induced seizures increase significantly at doses greater than 450 mg/day.

Clonidine, a noradrenergic alpha-2 agonist antihypertensive agent, has been shown to be effective for the treatment of ADHD but unlike guanfacine has not been FDA-approved (Connor et al. 1999). Modafinil, a novel wake-promoting agent that is FDA-approved for narcolepsy and shift work sleep, has been shown to improve ADHD symptoms in children, adolescents, and adults, albeit less so than stimulant medications (Biederman et al. 2006; Swanson et al. 2006; Taylor and Russo 2000). Although modafinil has some stimulant-like properties (e.g., promoting wakefulness), it has minimal reported abuse potential reported and has not been shown to be as effective as traditional stimulant medications and therefore was grouped with the nonstimulant second-line agents.

There are certain instances where nonstimulant medications would be considered first line, such as if a motor tic disorder is present or in the case of cardiovascular disease. While most treatment guidelines suggest avoiding nonstimulants for

those with a past or current substance abuse, there are certain clinical situations when it might be reasonable to use stimulants, particularly long-acting preparations, under controlled conditions.

123.2.6.3 Treatment of SUD Using Stimulants

Given that stimulants and several nonstimulant medications have been shown to be efficacious for ADHD, it is of clinical interest whether some of these medications are independently useful in treating substance use disorders. While this topic is beyond the scope of this chapter, certain conclusions can be drawn from the empirical literature. For well-selected patients with cocaine dependence or methamphetamine dependence, stimulant replacement can be safely given. There are very few instances of cardiovascular adverse events when agonists are given to a carefully screened cocaine abusers. Clinical trial eligibility excludes individuals at high medical and psychiatric risk and if introduced into the wider treatment community, more adverse events would likely to occur.

To date, the most promising results are with the higher-potency amphetamine analogs, or a combination of a dopaminergic intervention with a contingency management behavioral intervention (Mariani and Levin 2012). Notably, there are positive results from single-site trials, suggesting that stimulants, particularly amphetamines, may reduce cocaine use (Grabowski et al. 2004; Mooney et al. 2009). Modafinil and bupropion have also some clinical utility in specific subpopulations of cocaine and other stimulant abusers, but more work targeting these subgroups is needed (Anderson et al. 2009; Dackis et al. 2003; Elkashef et al. 2008).

Prescribing stimulants to active substance abusers needs to be handled cautiously and skillfully. Within a clinical trial, there is close monitoring and medication is administered in small quantities. In community settings, misuse or diversion would be more likely to occur and strategies on how to manage these risks are needed prior to initiating a course of stimulant therapy. While many clinicians avoid using stimulants in adolescents and adults with active substance abuse, there is a compelling rationale that by treating ADHD symptoms, substance use may diminish or cease, particularly if the stimulant has direct agonist effects on the substance being abused. As in the treatment of substance abusers with other psychiatric disorders, concurrently treating the symptoms of both the substance use disorder and the ADHD is more likely to produce a positive treatment outcome than treating one disorder alone. As more data are obtained, the utility of stimulants as an agonist approach will be determined and how to prescribe stimulants to active substance abusers will be further refined. To date, most recommendations are clinically derived with suggested approaches provided below.

123.2.7 Pharmacotherapy Selection for ADHD and Co-occurring SUD

The common wisdom is to avoid stimulants in substance abusers with ADHD. However, it remains unclear why this approach is so strongly endorsed. While it is

true that adolescents and college students who are prescribed stimulants are more likely to use their medication with other drugs of abuse or divert their medication, the majority do not. Further, there is no evidence that adults who are being treated for the substance abuse and ADHD simultaneously routinely abuse prescribed stimulants when closely monitored. Thus, it is preferable to examine the available data, albeit limited, to help guide clinical practice.

To date, there have been ten outpatient, double-blind, placebo-controlled treatment trials conducted in substance-dependent individuals. One trial included those that were primarily alcohol dependent (Wilens et al. 2008), one focused on nicotine-dependent individuals (Winhusen et al. 2010), two focused on primarily cocaine dependent (Levin et al. 2007; Schubiner et al. 2002), one focused on cocaine dependent while maintained on methadone (Levin et al. 2006b), one targeted methamphetamine abusers (Konstenius et al. 2010), and two entered patients with various substance dependencies but not one primary substance of abuse (Riggs et al. 2004; Thurstone et al. 2010). Four of the trials evaluated a nonstimulant medication. One trial evaluated bupropion in cocaine-abusing methadone-maintained ADHD patients (Levin et al. 2006b) and another evaluated atomoxetine in cannabis-dependent ADHD individuals (McRae-Clark et al. 2010); bupropion was not found to be helpful in reducing ADHD symptoms or substance use, while atomoxetine was better than placebo on ADHD secondary outcome measures, but not marijuana use. However, another trial found that atomoxetine was superior in reducing ADHD symptoms in alcohol-dependent individuals and outperformed the placebo group on some secondary alcohol outcome measures (Michelson et al. 2003).

Not surprisingly, because methylphenidate is a commonly used first-line treatment for ADHD, it has been studied more extensively. While methylphenidate showed promise in uncontrolled trials in reducing ADHD symptoms and cocaine use (Levin et al. 2006a; Somoza et al. 2004), double-blind trials have been mixed. In one trial, methylphenidate was superior to placebo in improving ADHD symptoms on some measures, but not others, and was not better than placebo in reducing cocaine use (Schubiner et al. 2002). In another trial, results were negative for both ADHD and cocaine use; although on a secondary outcome measure for cocaine (proportion of cocaine-positive urines over time), sustained-release methylphenidate was superior to placebo (Levin et al. 2006a). Finally, two recent trials evaluated OROS-methylphenidate for substance-abusing adolescents and adult nicotine-dependent individuals with ADHD. In the nicotine-dependent adults, OROS-methylphenidate plus a nicotine patch was superior to placebo plus a nicotine patch in reducing ADHD symptoms but not smoking cessation (Winhusen et al. 2010). The other trial conducted in adolescents found that OROS-methylphenidate was superior to placebo on some ADHD outcome measures, although not the primary one, but again, was not superior to placebo in reducing substance use (Riggs et al. 2011). An earlier trial with pemoline in adolescents found that pemoline was better than placebo in reducing some ADHD outcome measures but not substance use.

Importantly, none of these trials observed misuse or abuse of the prescribed medications. In fact, laboratory data suggest that amphetamine administration reduces cocaine choice in nontreatment-seeking cocaine-dependent individuals

(Rush et al. 2010). Despite concerns that prescription stimulant use may lead to increased craving for cocaine or amphetamine use, this effect has not been reported in the controlled clinical trials conducted to date. Taken together, the clinical trials using methylphenidate (and pemoline) have been mixed in reducing ADHD symptoms, with perhaps a "signal" in reducing cocaine use. Atomoxetine outperformed placebo in reducing ADHD symptoms and alcohol use in alcohol dependent but has not shown superiority over placebo with cannabis-dependent individuals. While prescription stimulant medications may be diverted for nonmedical use, clinical data suggests that the use of stimulants in a structured therapeutic context can be accomplished safely. Possible reasons for the modest response to medications for substance abusers with ADHD include (1) inadequate dosing, (2) less responsiveness if actively using substances, (3) lack of abstinence to clarify the ADHD diagnosis, (4) use of older, poorly absorbed sustained-release stimulant formulations, (4) additional comorbidities, and (5) poor compliance. Until these issues are addressed, it will be difficult to draw conclusions based on the available literature. Notably, there have been no published clinical trials evaluating amphetamine analogs for adult substance abusers with ADHD, despite a recent meta-analysis suggesting that amphetamines outperform methylphenidate products.

123.2.8 Non-pharmacologic Interventions for ADHD and Possible Approaches for Those with SUD

Whereas there is a fairly large literature evaluating various pharmacologic interventions for adult ADHD (and a much larger one for childhood ADHD), there remains limited data regarding the use of psychotherapies for ADHD adults and no trial has evaluated psychotherapy alone for ADHD adults with substance abuse. Common approaches used for childhood and adult ADHD and substance abusers include (1) contingency management, (2) cognitive-behavioral interventions, and (3) integrated pharmacologic and behavioral treatments. While contingency management approaches have been used in children and are highly successful when applied to adult substance abusers (Budney et al. 2006; Higgins et al. 1991), application of a contingency system for adult ADHD behaviors is not readily apparent. More often, it is often the family members, colleagues, or significant others who change their behaviors to accommodate the individual with ADHD. For example, a spouse may take charge of the finances and taxes or a co-worker or assistant will help organize their ADHD colleague's schedule or other work-related activities. At present, there have been no contingency management strategies that have been developed for ADHD adults with substance abuse.

Cognitive-behavioral therapy is an integral component of many addiction treatment programs, but it is not clear whether these approaches would work as well for those with comorbid ADHD. Cognitive interventions for children with ADHD were evaluated in the Multimodal Treatment Study of Children with ADHD (MTA Study 1999), and it was found that combined medication and behavioral treatment was not superior to medication management for core ADHD symptoms, but may have

provided modest advantages for non-ADHD symptom and positive functioning outcomes (Jensen et al. 2007). To date, there have been seven controlled psychotherapy trials conducted in adults with ADHD in which cognitive-behavioral, metacognitive therapy, and cognitive remediation have been studied (Vidal-Estrada et al. 2012). For all of these studies, some if not all of the patients were receiving ADHD medications. Often the patient samples had a partial response to medication and still had impairing ADHD symptoms. One of these studies was conducted in 86 adults with ADHD. Individuals were randomly assigned to either 12 weeks of cognitive-behavioral therapy or relaxation with educational support. Notably, treatment retention was high (92 %) and 81 % completed the follow-up assessments. Patients randomized to the 12 weekly individual CBT sessions had significant greater reduction in ADHD symptoms and improvements were maintained 6 and 12 months after study completion (Safren et al. 2010). This study is clinically relevant to substance abusers because their therapeutic response to ADHD medication is often modest. The addition of CBT that targets both the ADHD symptoms and substance abuse is likely to lead to enhance the benefits associated with pharmacotherapy.

Working with substance abusers with ADHD, Aviram et al. (2001) found that it is useful for therapists to identify the commonalities between the cognitive, behavioral, and physiologic symptoms associated with ADHD and those associated with drug use. Impairments from ADHD may lead to diminished self-esteem and depression, which in turn, may lead to drug use and further diminish the patient's coping abilities. The deficits must be countered in treatment by providing tangible coping skills and techniques, many of which are incorporated into the cognitive behavioral treatment model (ASAM 2009). This integrative approach has been applied successfully to substance abusers with bipolar illness (Weiss et al. 2007) and likely to have utility for adult substance abusers with ADHD.

123.2.9 Clinical Management of ADHD and Co-occurring SUD

Most clinical recommendations suggest that nonstimulants should be the first-line treatment for substance abusers with ADHD. However, it is often not clear whether this applies to anyone with a substance use history or to those with current substance abuse. Often, what is lost in these assertions is (1) what to do when a nonstimulant has not been effective for ADHD or cannot be tolerated for a particular patient; (2) the reality that nonstimulants have clinical utility but are often not as efficacious as stimulants; (3) the laboratory and clinical data findings that demonstrate that long-acting stimulants have lower abuse potential than immediate-release stimulants, albeit some potential for abuse; and (4) that there has been no evidence of abuse of long-acting stimulants prescribed for ADHD in substance abusers enrolled in clinical trials. While it is a clinical reality that some misuse and diversion will occur, particularly in substance abusers, this risk needs to be balanced against the risk of untreated or inadequately treated ADHD. Regardless of what class of medication is chosen, the appropriateness of the medication choice

should be regularly assessed based on the patient's clinical response and overall functional status. While it is not unreasonable to use atomoxetine or extended-release guanfacine as first-line treatments for active substance abusers with ADHD, the avoidance of stimulants, particularly long-acting formulations, may prevent a substantial number of individuals from receiving adequate treatment.

Although there are no clear-cut data to produce clinical guidelines, we would propose classifying patients with ADHD and substance abuse into three groups to help guide clinical choices. First, it is important to determine whether the patient has a current or past SUD. A remote history of substance abuse probably represents a low-risk group. However, patients, and when appropriate families, should be advised that their SUD history may increase their risk. Given that there is an increased risk, physicians might consider using extended-release preparations, monitor prescription renewal times, and closely monitor for evidence of substance use.

As described earlier, patients with ongoing substance use but not currently meeting criteria for abuse or dependence probably are at moderate risk for misuse (such as taking prescription medication in conjunction with other substances of abuse) or diversion of prescription stimulants. Compared to the low-risk group, there is a need for more frequent office visits, urine toxicology testing, and close attention to substance use patterns. For these patients, nonstimulants may be a reasonable first choice, but if stimulants are considered, then extended-release preparations are preferable. Patients with an active SUD represent a high-risk group in that they are at elevated risk for misuse or diversion of prescription stimulant treatment of ADHD. For this group, nonstimulant medications are likely to be chosen, but this should not preclude the use of stimulant medications in certain circumstances. For example, an extended-release stimulant may be indicated in an intensive structured and monitored outpatient treatment program (Riggs and Winhusen 2009; Winhusen et al. 2010).

There are several safeguards that may help reduce the likelihood of misuse and diversion. These include (1) maintaining careful prescription records, (2) frequent patient visits, and (3) use of extended-release formulations. It is important to explain to patients that urine toxicology screens will be conducted randomly, and if the patient does not show a significant reduction in alcohol or drug use, other treatment strategies will be needed. Further, patients should be encouraged to regularly take their medication rather than on an as-needed basis, to avoid intermittent palliation of symptoms. "Red flags" suggesting that there may be misuse, diversion, or abuse of prescription stimulants include frequent lost prescriptions or discordant pill counts, demands for immediate-release preparations, escalating doses, physiologic toxicology (hypertension, tachycardia, or chest pain), or psychosis.

Because there is an increased risk of stimulant misuse or diversion when ADHD patients have a co-occurring SUD, there needs to be an open dialogue about not misusing or diverting their medication. Moreover, patients should be told to safeguard their medication since other friends or family may steal the medication. While tailoring the clinical approach based on level of patient risk (low, moderate, or high) may mitigate risk if an abusable medication is prescribed, it will not eliminate it entirely. Good clinical judgment requires flexibility and a willingness to balance risk with therapeutic benefit.

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Personality Disorders and Addiction Disorders

124

Néstor Szerman and Lola Peris

Contents

Abstract

From Personality Traits to Addictive Disorders Substance use disorders (SUD) are highly prevalent in patients with personality disorders (PD) and vice versa.

Evidence for causal relationships between addictive disorders and PD can be derived from long-term longitudinal studies, epidemiological findings, genetics, and retrospective studies. Although they are inextricably linked, little is known about the role of a broad range of personality traits and disorders in the evolution of SUD and whether they differ according to substance.

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Biogenetic research has been confined largely to antisocial, borderline, and schizotypal personality traits and disorders. Understanding the neurobiological mechanisms by which certain personality traits may provide vulnerability to or resilience against SUD would help to develop strategies for SUD prevention.

The existence of addictive behaviors with regard to different substances probably suggests different phenotypes that should be defined for treating patients with this dual disorder. In that sense we must look for the integration of personality traits and substance use disorders via common psychopathological spectra based on common, biological dysfunctions.

Traditionally, both illnesses have been treated as separate conditions, but, in the last few years, the close connection between them has been increasingly acknowledged. Most SUD patients have pathological personality traits or disorders and often do not receive the appropriate diagnosis and treatment.

It is always necessary to search for a diagnosis of personality disorders and traits in patients with SUD. At the same time, a vigorous treatment should be simultaneously established for both psychopathological manifestations.

124.1 Introduction

The population with dual disorders/pathology (addiction and other mental disorders) is heterogeneous and the prevalence of comorbidity differs according to diagnostic groups. One of the overarching issues in relation to comorbidity is the nature of the connection between addiction disorders and other psychiatric disorders. The rapid development of technical advances in neuroscience has led to a better understanding of the molecular biology, neurotransmitter systems, and neural circuitry involved in substance use disorders and other mental disorders.

Addictive behaviors associated with other psychiatric disorders, which we refer to as dual pathology, are probably neurodevelopmental disorders (Szerman et al. 2013). These are disorders that begin very early in development and may present with different phenotypes, such as addiction-related or other psychiatric symptoms, at different stages during a person's lifetime.

From the clinical point of view, we know that one of the most relevant comorbidities is personality disorders and addictive behaviors. Substance use disorders (alcohol, nicotine, and other substances) are highly prevalent in patients with personality disorders (PDs) and vice versa and are associated with considerable health, economic, and social burdens (Hasin et al. 2011).

Various factors may contribute to the particularly strong association between lifetime diagnoses of personality disorders and increased rates of transition from substance use to substance use disorder (SUD) and other addictive behaviors. There is in any case a strong association between a lifetime diagnosis of any mental disorder and rates of transition from substance use to SUD. "Though this was true for all mental disorders, it was particularly true for personality disorders and psychotic disorders" (Lev-Ran et al. 2013). Moreover, reports from the NESARC

study sample show a high degree of personality disorders comorbidity within the DSM-IV clusters and between clusters (Grant et al. 2005).

As recently stated, axis I disorders should not have a strong or consistent association with persistent SUD. In contrast, antisocial personality disorder, borderline personality disorder, and schizotypal personality disorder seem to be significantly associated with SUD (Hasin et al. 2011).

Personality disorders and addiction disorders constitute a problematic area of psychiatry. In all current mental diagnostic and classification systems, these disorders are defined on a phenomenological basis. In the field of addiction disorders and personality disorders, there is the additional difficulty of there being many different and conflicting schools of thought about the nature of these conditions.

There has been substantial criticism of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), due to problems of diagnostic overlap, a lack of clear boundaries between "normality" and disease, a failure to take into account findings from new research, and also a lack of diagnostic stability over time (Zimmerman et al. 2011). Most neuroscientific evidence suggests that the neurobiology of psychiatric disorders, including personality disorders, does not seem to align with the current diagnostic classifications and categorical distinctions derived from Kraepelin's classic descriptions (DSM-IV or ICD-10). Current diagnostic categories may be inadequate. There are numerous recent studies suggesting that the biology of mental illnesses may fail to align neatly with the classic Kraepelinian classification that has served clinical practice and research for well over a century (Insel and Wang 2010). The prevailing "neo-Kraepelinian" diagnostic system only provides for a categorical diagnosis and therefore does not allow for the possibility of dual diagnosis. Also the current nosological approach does not provide a framework for internal (subthreshold symptoms) or external (comorbidity) heterogeneity of the different diagnostic categories (Szerman et al. 2013). Finally, the majority of studies have not tested multidimensional models of mental disorders and we need to move towards the conceptualization of new models of brain disorders.

124.2 Personality Disorders and Addiction Disorders

A high level of comorbidity that cannot be explained by conceptual or measurement artifacts strongly suggests that the co-occurrence of addiction disorders and personality disorders is not solely due to random or coincidental factors. It seems reasonable to explore the assertion that both conditions are in some way causally linked. Evidence for causal relationships between addiction disorders and PD can be derived from long-term longitudinal studies, epidemiological findings, genetics, and retrospective studies (Verheul et al. 2009). They are inextricably linked and little is known about the role of a broad range of personality traits and disorders in the progression of SUD and whether they differ according to substance.

124.2.1 Primary Substance Use Disorder Model Versus Primary Personality Disorder Model

Currently there is no direct evidence supporting **the primary substance use disorder model** (it postulates that substance abuse contributes to the development of PD) and there is in fact some indirect evidence against it (Verheul et al. 2009).

The primary personality disorder model describes a comorbid relationship in which pathological personality traits based on certain biological conditions contribute to the development of an addiction disorder. This model has received the strongest empirical support, showing multiple symptomatic pathways from personality to addiction: behavioral disinhibition, stress reduction, and reward sensitivity (Verheul et al. 2009).

124.2.2 Changes in the Conceptualization of Addictive Behaviors and Personality Disorders from a Biological Perspective

Is it possible to explain complex mental and behavioral disorders such as addiction and personality disorders at a biological level?

Biological psychiatry has been based on the desire to uncover the relationship between mind and brain through systematic research. To understand a psychiatric disorder, we need to know why the pathology causes the behavioral disturbance, the neural structures implicated in the pathology, and the cause of the dysfunction in the neural structures. Genes, neural bases, and environment are no longer viewed as separate entities but rather as being intimately interconnected, as in a continuum. Nevertheless in relation to the abovementioned evolution, it may seem that psychiatry in general and particularly in relation to addiction and personality disorders does not follow the progress of biological research with the same confidence as other areas of medicine.

- Addiction Disorders

  The term "addiction" should be used instead of the term "dependence" as described in DSM-IV to avoid confusion with physical dependence, which is neurobiologically and clinically distinct from addiction. "We refer to addiction as the phenotype characterized by the compulsive administration of the drug and the loss of control over its intake despite its adverse consequences to the individual" (Volkow and Muenke 2012).

  The diagnostic concept of dependence in DSM-III (1980) was focused around neuroadaptation to drugs (evidence of acquired tolerance and/or withdrawal symptoms). This concept was revised in DSM-III-R (1987), which focused on a behavioral syndrome including dyscontrol, salience and neuroadaptation, as well as compulsive behavior (Sellman 2009).

  Progress in neurobiology has provided a new way to identify the neurobiological mechanism involved in the development of drug addiction.

  Over the past decades, differing biological addiction theories have been proposed by researchers (Badiani 2011), but all psychoactive substances with abuse potential

have a counterpart or correspond to some endogenous system such as the opioid system, the endocannabinoid system, the cholinergic-nicotinic system, the dopaminergic system, and so on. An inherited or acquired deficiency in these neurobiological systems and circuits may explain addictive behavior and other psychiatric symptoms including personality traits or disorders (Szerman et al. 2013).

Substance use disorders are considered in most investigations as a function of time, type, or amount of substance consumed, although addictive drugs do not have to precipitate addictive behaviors or drug dependence in most individuals (Feltenstein 2008).

In "the classic addiction perspectives" (Swensen and Moal 2011), the emphasis is often on the effects of substances on the brain, creating the impression that dual disorders are a natural consequence of these substances (Nestler et al. 2005). This old model of addiction assumes that drugs of abuse "hijack" the brain's reward system, disrupting the normal behavioral responses to natural rewards (Welberg 2011).

The classic addiction paradigm based on drug-induced neuroplasticity and on acquired vulnerability, largely dominant in laboratory research, has changed to a new "individual-centered" paradigm approach that takes individual variation to be the focal point: the strong association of addiction with certain personality traits (Volkow et al. 2011) or comorbid mental disorders (Swensen and Moal 2011). Basic neuroscientific research has demonstrated the key roles of biological and genetic/epigenetic factors in an individual's propensity to these disorders including the propensity to behavioral addictions. A challenge for the future is to understand the development of compulsivity at neurochemical level not only in relation to drugs but also in the range of emerging behavioral addictions (Sellman 2009) and compulsive traits.

The inclusion in the next DSM-5 of behavioral addictions like pathological gambling has to change our way of understanding and dealing with addictions. From a neurobiological perspective, we should not maintain an explanatory model that only provides results on neuroadaptation to the continued use of substances of abuse.

- Personality Disorders

> It's time to go back to the beginning, to Darwin, and build a logical structure based on universal principles of evolution. (Millon)

The Different, Current, Theoretical Frameworks for Personality Disorders (PD):

For years personality disorders have hung around like orphans (axis II), but personality problems are not exactly new. In fact, the focus for personality disorders will depend largely on the perspective from which they are approached:

1. Psychodynamic model: the PD conceived as a result of internal organization.
2. Trait-based model: it focuses on the type of behavior and interpersonal relationships.
3. Biological model: the PD as being organized around biogenetic factors.
4. Sociological model: personality is formed through social circumstances and PDs appear under harmful circumstances.

The focus for personality disorders will depend largely on the perspective from which they are approached. Until recent years there was only the psychological approach, and the explanation of personality disorders was based on studies of the psychological mechanisms and interactions with the environment. The dysfunctional biological bases were excluded or had not yet been considered. The identification of neural correlates of PD may have profound implications on our basic understanding of the biological substrates underlying human behavior.

Biogenetic and heritability research has been confined largely to antisocial, borderline, and schizotypal personality disorders, with very little research specifically concerning the other DSM-IV personality disorders (Nigg and Goldsmith 1994).

Longitudinal studies indicate that PDs as syndromes exhibit consistency over time but show rates of improvement that are inconsistent with their DSM-IV definitions (Skodol et al. 2009). On the other hand, considerable research has shown excessive co-occurrence among PDs diagnosed using the categorical system of DSM-IV (Zimmerman et al. 2005) and all PD categories have arbitrary diagnostic thresholds without empirical evidence for setting the boundaries between pathological and normal personality functioning. Moreover, comorbidities between different diagnostic categories are probably defining different phenotypes that should be taken into account when diagnosing and treating these patients.

Over the last century, scientific consensus has been reached on a taxonomic model of personality traits. Personality can be thought of as a set of characteristics that influence people's way of thinking, feeling, and behaving in a variety of settings. A variation in personality traits is predictive of many outcomes in life including mental health, mental disorders, and, within this, substance use disorders (De Moor et al. 2012).

For this purpose, a more encompassing trait system for the diagnosis of personality disorders has been proposed in the DSM-5 (Sect. III). Prototypical disorders are characterized by core impairments in personality functioning and different levels of abnormal personality traits grouped in six broad dimensional domains: negative emotionality, introversion, antagonism, disinhibition, compulsivity, and schizotypy. Personality traits have been shown to interact with environmental cues to modulate biological responses.

Personality traits are more stable than PDs and predict stability and change in personality disorders. Personality traits are often related to psychopathology and investigating their neural substrates may inform etiological and pathophysiological models of psychiatric disorders (Woodward et al. 2011). In this sense, the existence of addictive behaviors with regard to different substances probably suggests different phenotypes that should be defined for treating patients with this dual disorder: integration of personality traits and substance use disorder via common psychopathological spectra based on common, biological dysfunctions.

Little is known about the neurobiological correlates of human personality traits and how they relate to substance abuse or dependence. Nonetheless evidence is increasingly growing, for example:

– Variability in harm avoidance (a temperament trait associated with sensitivity to aversive and non-rewarding stimuli, higher anticipated threat, and negative

emotions during stress as well as a higher risk for affective disorders), a trait that can be explained by differences in the activity of the μ-opioid system (Tuominen et al. 2011).
- The evidence that borderline PD patients suffer from a definite abnormality in opioid activity (New and Stanley 2010).
- A role for functional mu-opioid receptor gene polymorphisms in the expression of attachment behavior in human subjects, especially as a function of separation from the caregiver (Barr et al. 2008).
- Positive emotionality (a personality construct indicated by well-being, achievement/motivation, social competence, and closeness, which may relate to global cortical processes that are active during resting conditions, introspection, or mind wandering) has been associated with striatal dopamine D2 receptor availability in healthy controls and is considered a trait that protects against substance use disorders (Volkow et al. 2011).
- Neural mechanisms of anger regulation as a function of genetic risk for violence: vulnerability to aggression in carriers of the low-MAOA genotype is supported by decreased middle frontal response to the word "no" and the unique amygdala/thalamus association pattern in this group with anger reactivity but not anger control (Alia-Klein et al. 2009).
- The studies show the difficulties in identifying common genetic variants that influence complex phenotypes such as personality traits. Genome-wide association studies (GWAS) may reveal these variants in a large meta-analysis. The identification of these genetic variants that account for the heritability remains an important goal that will enable the understanding of the biological process underlying personality as well as psychiatric disorders, including addiction disorders and personality traits (GWAS 2009).

124.2.3 A Need to Diagnose Addiction Disorders and Personality Disorders

In general population research, all ten DSM-IV (and DSM5) personality disorders were shown to have strong associations with alcohol and tobacco dependence and with drug use disorders (abuse and dependence) (Hasin et al. 2011).

The association between personality disorders and substance use disorders appears to differ according to the specific personality disorder. Traditionally, both illnesses have been treated as separate conditions, but in the last few years, the close connection between the two has been increasingly acknowledged. Most SUD patients have pathological personality traits or disorders and often do not receive the appropriate diagnosis and treatment. It is much more difficult to assess the personality dysfunctions of patients with ongoing SUD. A successful diagnosis is essential for well-adapted and high-quality treatment; therefore, it is extremely important that all the disorders of a patient are diagnosed (Langås et al. 2011).

According to more recent epidemiological and biological studies and also the newest DSM-5 proposals, we will focus on the three major personality disorders in

relation to addictive behaviors: schizotypal (SPD), borderline (BPD), and antisocial (ASPD) personality disorders. Other personality disorders are also significantly associated with persistent SUD, but in a less consistent manner.

124.2.4 Schizotypal Personality Disorder and Addiction Disorders

Schizotypal personality disorder is the prototypical schizophrenia spectrum condition, sharing similar phenomenological, cognitive, genetic, physiological, neurochemical, neuroanatomical, and neurofunctional abnormalities with schizophrenia (Fervaha and Remington 2012). Nonetheless, despite the similarities in neurodevelopmental alterations at frontal and temporal levels, they are milder than those that are found in schizophrenia because of the ability to recruit other related brain regions to compensate the dysfunctional ones.

These patients are also less vulnerable to psychosis, because of the existence of protective factors that mitigate the subcortical DA activity. Despite its phenomenological proximity to schizophrenia, SPD has been recognized as a distinct disorder, the criteria of which represent the persistent maladaptive patterns of a personality disorder rather than the overt, symptomatic break from reality of a psychotic disorder. SPD also shares phenomenological features with schizoid and paranoid personality disorders.

An important factor supporting the inclusion of SPD as a prototypical DSM-5 personality disorder is the fact that many of its current criteria have been validated by external validators (e.g., neurochemical, neuropsychological, functional, and structural findings) (Chemerinski et al. 2012).

Schizotypal personality traits encompass a broad range of personality characteristics and experiences, including unusual perceptions and beliefs, social anxiety or withdrawal, and disorganized thoughts or behaviors. These traits cluster into positive, negative, and disorganized factors that are conceptually similar to the symptom dimensions of schizophrenia. The expression of these traits ranges from benign, odd perceptual experiences or beliefs to more severe symptoms.

Some recent research found that two factors were specific to SPD: a cognitive-perceptual factor (ideas of reference, magical thinking, and unusual perceptual experiences) and an oddness factor (odd thinking and speech, constricted affect, and odd appearance or behavior). The criteria belonging to these factors had appropriate psychometric properties. Support for a consistent factor that reflected interpersonal problems was not found and the authors postulated that interpersonal dysfunction was secondary to the two primary SPD factors (Hummelen et al. 2012).

According to Fenton et al. (2012), ideas of reference and social anxiety were the strongest schizotypal criteria predictors of drug use disorder persistence, and according to Buckner et al. (2012), social anxiety might be a risk factor for cannabis dependence.

The relationship between schizotypal personality disorder and tobacco is also receiving increasing attention. A recent study examined the relationship between sub-factors within schizotypal symptoms founding a relationship between

smoking and eccentric behavior and odd speech but not between other domains (Esterberg et al. 2009). Another study examined the prevalence of tobacco addiction and its associations with personality disorders among smokers, and although all PDs were significantly associated with tobacco dependence, when sociodemographic factors were controlled, only schizotypal, borderline, narcissistic, and obsessive-compulsive PDs were associated with tobacco addiction after adding controls for axis I and other axis II disorders (Pulay et al. 2010).

124.2.4.1 Cannabis Use Disorder and SPD: A Long-Lasting Debate

There may be a developmental process in the relationship between cannabis use and schizotypal symptoms (Bailey and Swallow 2004). Cannabis acutely increases schizotypy, and chronic use is associated with elevated rates of psychosis. Cannabis use may reveal an underlying vulnerability to psychosis in those with high schizotypal traits.

An important group of cannabis users shows dimensions of schizotypy, which provides further evidence that cannabis use is associated with increased levels of psychosis-related personality traits. Also, higher cognitive-perceptual schizotypy was selectively associated with cannabis use, although the disorder was associated with greater use of alcohol and tobacco too (Esterberg et al. 2009).

Findings suggest that regular cannabis users are significantly more prone to cognitive and perceptual distortions as well as disorganization (but not interpersonal deficits) than non-regular users and those who have never used, and the onset of schizotypal symptoms generally precedes the onset of cannabis use (Schiffman et al. 2005). This was the only study to address a temporal order in the sense that schizotypal symptoms preceded cannabis use, suggesting that this association is not an artifact of cannabis effects. Meanwhile, other researchers found that early SPD symptoms could not fully explain the association between early cannabis use and later schizotypal symptoms (Anglin et al. 2012).

Interestingly, in another recent study, scores from a measure of schizotypal traits were used to separate 1,665 young adults into schizotypy, non-schizotypy, and "unconventional" groups. "Nearly a quarter of the schizotypy group endorsed cannabis use at least weekly, a rate nearly two to four times that of the other groups. The schizotypy group also reported a much greater frequency of cannabis-related problems compared to the other groups. Despite this, interest in treatment for cannabis use in the schizotypy group was not elevated. Curiously, 85 % of individuals in the schizotypy group reported interest in psychological/psychiatric treatment more generally but not cannabis dependence treatment. Cannabis use was not associated with abnormal patterns of positive or disorganized schizotypy traits in the schizotypy group relative to the other groups but it was associated with lower severity of negative traits" (Cohen et al. 2011).

Another controversial issue is the "amotivational syndrome." This syndrome has been described as a form of chronic cannabis intoxication, although there is no scientific evidence to prove its existence, caused allegedly by cannabis. Although

there are individuals with genetically determined schizotypal traits, with subclinical psychopathological features such as anomalous subjective experiences, negative symptoms, anhedonia, decreased vitality, apathy, associability, restricted affect, and subpsychotic formal thought disorder (Raballo and Parnas 2011), they probably suffer a vulnerability to cannabis use disorder. The negative-like symptoms and cognitive deficits of SPD have also been assessed with the use of external validators. These are mostly associated to the frontoparietal-temporal circuit dysfunction prevalent in this disorder.

124.2.4.2 Why Do These Patients Feel Such a Fatal Attraction to Cannabis?

Data reported so far clearly indicate the presence of a dysregulation in the endocannabinoid system (both in terms of cannabinoid receptors and endocannabinoid ligands) in animal models of psychosis as well as in schizophrenic patients (Zamberletti et al. 2012).

Anandamide (endocannabinoid ligand) and also exogenous cannabis, both attenuate the hypothalamus activation produced by stress. This adjustment depends on the availability of the anandamide precursor, arachidonic acid, which seems to be low in schizotypy subjects (Monterrubio and Solowij 2006).

Recent research suggests that delta-9-tetrahydrocannabinol (THC, the main psychoactive component of cannabis) increases dopamine levels in several regions of the brain, including striatal and prefrontal areas, showing the interactions between THC, endocannabinoids, and dopamine in cortical as well as subcortical regions (Kuepper et al. 2010) implicated in schizotypal disorder. Exploratory analyses of Schizotypal Personality Questionnaire factor scores revealed correlations between disorganized schizotypal traits and dopamine release in the striatum, thalamus, medial prefrontal cortex, temporal lobe, insula, and inferior frontal cortex produced by amphetamine. Amphetamine-induced dopamine release may be a useful endophenotype for investigating the genetic basis of schizotypal spectrum disorders (Woodward et al. 2011).

Based on these observations, the pharmacological modulation of the endocannabinoid system has been taken into account as a new therapeutic possibility for psychotic disorders and could perhaps be considered for this dual disorder: schizotypal disorder and cannabis use disorder.

124.2.5 Borderline Personality Disorder and SUD

Borderline personality disorder (BPD) is a complex, serious psychiatric disorder characterized by pervasive instability in regulation of emotion, self-image, interpersonal relationships, and impulse control, and it is associated with severe functional impairment (APA 1994).

The reported prevalence is 15–25 % in clinical settings (the most prevalent PD in clinical settings) and 1.4–5.9 % in the community and it is equally prevalent in men as in women. These figures indicate that a large number of people with this disorder

are undiagnosed and untreated, while according to studies such as the McLean Study of Adult Development (2005) and the Collaborative Longitudinal Study of Personality Disorders (2005), BPD has an unexpectedly good course, contrary to what was previously imagined (Gunderson 2009).

BPD is the personality disorder with the greatest SUD co-occurrence, together with antisocial personality disorder (ASPD). Cross-sectional studies have found that 23–84 % of BPD patients report meeting criteria for some SUD, and up to 65 % of substance users in treatment meet criteria for BPD (Trull et al. 2000). A 10-year follow-up study has shown that although 90 % of BPD patients meeting criteria for a SUD at baseline experienced a remission, recurrences and new onsets were less common but always more frequent than in axis II comparison subjects (35–40 % vs. 21–23 %) (Zanarini et al. 2011).

New onsets of SUD do not differ significantly between remitted and non-remitted BPD patients. Even when remitted, they seem to have a higher vulnerability than patients with other PDs (with the likely exception of ASPD) to the development of SUD. This conclusion is consistent both with the concept of shared etiological factors between BPD and SUD as a spectrum relationship and with the "clinical wisdom that substance abuse is a particularly hazardous form of comorbidity for patients with BPD" (Walter et al. 2009).

If Cluster B is considered as having an independent risk for the development of SUDs (Cohen et al. 2007), many of the core features of BPD are also independent risk factors for their development. Both impulsivity and affective dysregulation/negative emotionality have been identified as key vulnerability factors in the development and maintenance of addictive disorders (Lubman et al. 2011; James and Taylor 2007).

As already stated, BPD, together with SPD and ASPD, seem to be the only axis II disorders associated with persistent SUD, while no axis I disorder shows this kind of association. Identity disturbance and self-damaging impulsivity are the strongest BPD criteria predictors of persistence (Fenton et al. 2012; Hasin et al. 2011).

124.2.5.1 The Role of Negative Emotionality and Impulsivity in the BPD-SUD Relationship

Both emotional dysregulation and impulsivity are core aspects of BPD pathology and probably of SUD comorbidity.

Impulsivity has for a long time been considered the most relevant factor in relation to drug addiction. The amount of published research is impressive and the advances in neurobiological techniques in the last decade have helped to deepen and focus knowledge on a very complex subject, progressively helping to clear up its still debated role in the addictive process and in BPD.

One important factor that worsens impulsive behaviors and impulse control deficits in some BPD patients is the phenotype with comorbid attention-deficit/hyperactivity disorder (ADHD). Well-observed impulsive behaviors might be explained by comorbid ADHD or may be the consequence of dysregulation of BPD salient emotions (Sebastian et al. 2013).

Advances in research indicate that impulsivity is a personality trait known to be related to greater vulnerability to SUD, along with novelty seeking and negative emotionality, while positive emotionality (PEM) is associated with resilience. Striatal D2 receptors modulate activity in the orbitofrontal cortex (OFC) and cingulate, two brain regions that process natural and drug rewards. In healthy controls, PEM has been associated with striatal dopamine D2 receptor availability. It was also positively correlated with the OFC and cingulate, as well as with other frontal, parietal, and temporal regions. As dysfunction of the OFC and cingulate is a hallmark of addiction, these findings support a common neural basis underlying the protective personality factors and brain dysfunction that lie beneath substance use disorders (Volkow et al. 2011).

Borderline personality disorder is characterized by a lack of effective regulation of emotional responses. Emotion dysregulation in BPD involves a dysfunction of the frontolimbic systems supporting negative emotionality. Deficient processing of negative emotions in BPD might then be related to an abnormal reciprocal relationship between limbic structures representing the degree of subjectively experienced negative emotion and anterior brain regions that support the regulation of emotion (Ruocco et al. 2013). Although human affective responses appear to be regulated by limbic and paralimbic circuits, much less is known about the neurochemical systems involved. The mu-opioid neurotransmitter system is distributed in and regulates the function of brain regions centrally implicated in the affective processing of an experimentally induced negative affective state (Zubieta et al. 2003).

124.2.5.2 BPD and the Opioid System

The role of the opioid system in BPD is a source of fruitful research.

Based on the key role of the central opioidergic system in addiction, recent research has investigated the relationship between certain personality traits that are supposed to be relevant in addiction and the opioid receptor status in healthy subjects. In such subjects, certain personality traits (novelty seeking, harm avoidance, reward dependence, and persistence), which might be predisposing for addictive behavior, are correlated to the opioidergic neurotransmission in core structures of the human reward system (Schreckenberger et al. 2008).

The opioid system regulates affective and sensory components of pain (Zubieta et al. 2001), as well as social exclusion, separation, and abandonment, particularly within perceived rejections. From an evolutionary perspective, it is not surprising that the neurocircuitry and neurochemistry of physical pain overlaps with that involved in complex social emotions (Stein et al. 2007).

Reduced pain sensitivity has been experimentally confirmed in patients with BPD, who also tolerate higher temperatures. In the study of Schmahl et al. (2006), pain stimulation produced an increased response in the dorsolateral prefrontal cortex and deactivation in the anterior cingulate and the amygdala, brain areas involved in the cognitive and affective evaluation of pain.

Approximately 60 % report not feeling pain during acts of self-mutilation such as cutting or burning. BPD self-mutilating patients who experience analgesia during self-injury show an increased threshold for pain perception even in the absence of

distress; it was postulated that this may reflect a state-independent increased pain threshold which is further elevated during stress (Bohus et al. 2000). One approach to self-injury in BPD patients is that it represents a method of endogenous opioid generation.

In BPD patients, symptoms of perceived rejection and loss often serve as triggers to impulsive, suicidal, and self-injurious behaviors, affective reactivity, and angry outbursts, suggesting that the attachment and affiliative system may be implicated in this disorder. Neuropeptides, including opioids, play a crucial role in the regulation of affiliative behaviors and thus may be altered in BPD (Stanley and Siever 2010).

Hypersensitivity to negative stimuli and excessive stimulation of negative affect are linked to increased brain activity in the amygdala and related brain structures, together with an orbital, prefrontal, and anterior cingulate hypoactivity (New et al. 2007). The amygdala, implicated in emotional responses and information evaluation and regulation, has a high concentration of mu-opioid receptors. In BPD, there are decreased basal opioid levels, balanced by an upward regulation of mu-opioid receptors. This decreased basal level would express in nuclear BPD symptoms: chronic dysphoria and emptiness and self-harm behavior, while releasing opioids, might facilitate relief (Stanley and Siever 2010).

Some important research stated that there are differences between patients with borderline personality disorder and comparison subjects in baseline in vivo mu-opioid receptor concentrations and in the endogenous opioid system response to a negative emotional challenge, which can be related to some of the clinical characteristics of patients with borderline personality disorder. The regional network involved is implicated in the representation and regulation of emotional and stress responses (Prossin et al. 2010).

Interestingly, high impulsivity and low deliberation scores have been postulated as being associated with significantly higher regional mu-receptor concentrations and greater stress-induced endogenous opioid system activation; effects were obtained in prefrontal cortex, OFC, anterior cingulate, thalamus, accumbens, and basolateral amygdala (all involved in motivational behavior and the effects of drugs of abuse) (Love et al. 2009). Research results concluded that individual differences in the function of the endogenous mu-receptor system predict personality traits that confer vulnerability to or resilience against risky behaviors such as the predisposition to develop substance use disorders. These personality traits are also implicated in psychopathological states (such as personality disorders).

124.2.5.3 BPD and Alcohol and Opioid SUD

The prevalence of BPD in heroin-dependent individuals is very high. A cohort of 495 heroin users enrolled in the Australian Treatment Outcome Study and criteria for BPD were met by 45 % of the cohort (Darke et al. 2005).

Also there is a high degree of comorbidity between borderline personality disorder (BPD) and alcohol use disorders. The research suggests a negative synergy between BPD and alcohol use disorder. In some recent epidemiological community

research, antisocial, borderline, histrionic, and narcissistic personality pathology factors were significantly associated with increased risk for alcohol use disorder (Agrawal et al. 2013).

Patients with BPD tend to abuse substances that target mu-opioid receptors, such as alcohol and opiates, substances that likewise provide relief from their suffering and discomfort. Shared vulnerability between opiate and alcohol addiction and BPD could be linked to an underlying dysregulation of neuropeptides, including opioids, which play a critical role in regulating affiliative behavior and a sense of well-being.

Specifically, alcohol-induced release of β-endorphins stimulates μ-opioid receptors (MORs), which is believed to cause dopamine release in the brain reward system. It has been suggested that individual differences in opioid or dopamine neurotransmission are responsible for enhanced liability to abuse alcohol (Spreckelmeyer et al. 2011).

Alcohol use may be viewed as an attempt to regulate negative emotional states through the regulation of the opioid system. Not all BPD patients are drinkers, but BPD drinkers showed higher within-person variability for the most intense negative affects than BPD non-drinkers (Jahng et al. 2011).

Future research could focus on normalizing opioid dysregulation, in addition to evidence-based psychotherapy, in an effort to improve interpersonal functioning.

124.2.6 Antisocial PD and SUD

Antisocial personality disorder (ASPD) is highly associated with persistent substance use disorders, mainly alcohol, cannabis, and tobacco use (Hasin et al. 2011).

In addition to the full ASPD syndrome, which requires both childhood conduct disorder and the adult features, other antisocial behavioral syndromes, including conduct disorder (CD) alone without the adult syndrome, and the adult antisocial behavioral syndrome without childhood CD (AABS) are also frequently diagnosed in patients with SUD (Mariani et al. 2008).

CD is a disorder that occurs during childhood and adolescence and is defined by rule-breaking, aggressive, and destructive behaviors. Progression from CD to ASPD is the norm and not the exception (Gelhorn et al. 2007) and we need to have in mind other clinical categories (different phenotypes) such as attention-deficit/hyperactivity disorder (ADHD) and SUD, to discern possible commonalities.

ASPD criteria focus on antisocial behaviors rather than on personality traits central to traditional conceptions of psychopathy. Psychopathy is a disorder, defined by Hare's Psychopathy Checklist – Revised (PCL–R) as being characterized in part by a diminished capacity for guilt, remorse, and poor behavioral control (Hare et al. 1991). Conceptualizations of psychopathy are not the same as diagnoses of conduct disorder or antisocial personality disorder. As such, only around 20–50 % of patients with ASPD also meet the criteria for psychopathy. Recent research strongly reinforces the suggestion that psychopathy is a neurobiological condition and these data maintain diagnostic precision (Blair 2012). Although the

neuropathological basis of psychopathy has not been clearly established, psychopaths have a significantly thinner cerebral cortex in different brain regions, mainly in the left insula. These neurostructural differences were not due to differences in age, IQ, or substance use disorders (Ly et al. 2011).

Strong associations between conduct disorder, attention-deficit/hyperactivity disorder, antisocial personality disorder, and substance use disorders seem to reflect a general vulnerability to externalizing behaviors. Recent studies have characterized this vulnerability on a continuous scale, rather than in distinct categories (Witkiewitz et al. 2013).

Patterns of genetic, environmental, and phenotypic relationships between antisocial behavior and substance use disorders indicate the presence of a common externalizing liability. Research regarding etiology, assessment, and treatment of externalizing disorders should target externalizing liability over a range of severity (Markon and Krueger 2005).

In that sense, considering the utility of endophenotypes, such as impulsivity, and using them "transdiagnostically" across disorders, such as ADHD, substance abuse, and ASPD, would help to achieve better diagnoses and treatment.

Psychopathy and SUD are highly prevalent in incarcerated populations. Recent research found that high impulsivity indirectly mediated the relationship between psychopathy and stimulant dependence meanwhile low anxiety sensitivity indirectly mediated the relationship between psychopathy and opioid dependence. Finally, impulsivity indirectly and inconsistently mediated the relationship between psychopathy and alcohol dependence. These results suggest that individuals with psychopathic traits are at increased risk of misusing certain drugs due to underlying personality-based differences (Hopley and Brunelle 2012).

The specific psychopathic trait, callous-unemotional (CU), is associated with more antisocial behavior, and those patients are at the highest risk of recurrent alcohol and cannabis use. Nevertheless the conduct disorder is probably more relevant than the CU traits in relation to SUD (Charles et al. 2012).

Deceitfulness and lack of remorse were the strongest antisocial criteria predictors of drug use disorder persistence (Fenton et al. 2012), while early-onset alcohol abuse and conduct disorder predicted adult ASPD (Khalifa et al. 2012).

124.2.6.1 ASPD and Alcohol Use Disorder

Among people with alcohol use disorder, ASPD is related to a more severe presentation and course of the disorder, such as an earlier age at onset and more rapid progression to dependence. Cloninger stated that alcoholics with an earlier age of onset (alcoholics type II) have relatively greater psychopathology than those with later onset (alcoholics type I). Alcoholism type II generally begins during adolescence and alcohol consumption frequently is accompanied by fighting and arrests. For type II alcoholics, who are primarily characterized by high novelty seeking, alcohol use is motivated by the desire to induce euphoria. This desire, which may also lead to abuse of other drugs, generally begins during adolescence or early adulthood (Cloninger 1987). Also type II alcoholics were

characterized by greater severity of alcohol-related problems, childhood behavioral problems, craving, hostility and antisocial traits, and poor social functioning (Johnson et al. 2000). Other researchers detected differences between type I and type II alcoholics not only in their age at onset and the type of alcohol-related problems but also in certain neurobiological markers: for instance, preliminary results from diagnostic groups with a relatively small number of subjects and substantially different mean ages for each group suggest that the endogenous cannabinoid system may be hyperactive in type II alcoholics and hypoactive in type I alcoholics (Lehtonen et al 2010).

ASPD is considered to be an important cofactor in the pathogenesis and clinical course of alcohol dependence, but some studies have highlighted that the onset of ASPD characteristics preceded that of alcohol addiction by approximately 4 years, and this finding suggests that in patients with ASPD, alcohol dependence might be a secondary syndrome (Bahlmann et al. 2002). In a more recent study from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) in terms of alcohol consumption behavior, the young antisocial subtype significantly reduced their risk drinking days between NESARC study Wave 1 and Wave 2 (in this second wave, interview was conducted approximately 3 years later) (Moss et al. 2010).

Few studies have investigated the combined association between ASPD and alcoholism in relation to neuropsychological function. Alcohol-dependent patients with ASPD exhibit decision-making deficits and personality traits characterized by impulsive and antisocial tendencies that are more pronounced than alcohol-dependent patients without ASPD (Miranda et al. 2009). Another study that examined the influence of ASPD symptoms and alcoholism on tests sensitive to frontal brain deficits found that alcoholism and ASPD were significant predictors of frontal system and affective abnormalities suggesting that the combination of alcoholism and ASPD leads to greater deficits than the sum of each (Oscar-Berman et al. 2009).

124.2.6.2 ASPD and Stimulant Drug Addiction

Research tells us that symptoms or traits of ASPD, such as deficits in executive function and response regulation, as well as anxious-impulsive personality traits, may represent endophenotypes associated with the risk of developing cocaine and amphetamine dependence (Ersche et al. 2012b). Recent research found abnormalities in frontostriatal brain systems implicated in self-control in both stimulant-dependent individuals and their biological siblings with no history of chronic drug abuse. These findings support the idea of an underlying neurocognitive endophenotype for stimulant drug addiction (Ersche et al. 2012a).

A commonly held perception is that cocaine use is more highly associated with antisocial behavior than cannabis use, although a comparison of ASPD rates among individuals seeking treatment for cocaine and cannabis dependence did not reveal significant differences between the two groups of patients (Mariani et al. 2008).

It is suggested that neural structures implicated in psychopathic pathology also include the amygdala and orbitofrontal cortex (OFC). One feature associated with

psychopathy is substance misuse. This could contribute to apparent impairments. SUD could reflect the lifestyle of the individual with psychopathy where substance misuse has interacted with the fundamental pathology to produce additional OFC pathology (Blair 2003). However, frontal systems dysfunction is present prior to stimulant-abuse onset (Winhusen et al. 2013).

Young adults under treatment with SUD and comorbid ASPD do not necessarily have poorer retention or worse substance use outcomes compared with SUD young adults who do not have ASPD, when treated according to a well-defined behavioral therapy protocol (Easton et al. 2012).

124.3 Conclusion

Although significant advances have been made over the past several decades in the development of effective research for addictions and personality disorders, they remain a substantial public health problem. The development of new neuroscientific methodologies to assess brain structure and function provides an exciting opportunity to apply these tools in order to understand and improve treatments.

Clinicians should have increased expectations that a patient with a SUD may have a co-occurring pathological personality trait or disorder. The consistent findings on the association of schizotypal, antisocial, and borderline personality traits or disorders with persistent SUD indicate the importance of these disorders and their neurobiological basis in understanding the course and treatment of SUD.

Understanding the neurobiological mechanisms by which certain personality traits may provide vulnerability to or resilience against SUD would help to develop strategies for SUD prevention.

Future research may enable the neurobiological link between personality traits and addiction to different substances of abuse to be understood.

From a dimensional perspective, we must consider personality traits and their combination with other syndromic disorders (such as ADHD) along with SUD, in an effort to define clinical phenotypes that should guide more individualized treatment.

It is necessary to search for a diagnosis of personality disorders and traits in patients with SUD and this dual diagnosis should not distract us from simultaneously starting vigorous treatment for both psychopathological manifestations.

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Overview of International Issues in Comorbidity

125

Pedro Ruiz and Ihsan M. Salloum

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125.1 Introduction

The role and concept of "comorbidity" has radically changed in the field of substance abuse in recent years. No longer the concept of comorbidity as two independent or parallel factors playing a role within each other in the presence of substance abuse condition is considered the prevailing factor in the understanding and conceptualization of "substance abuse" or "addictive disorders." Actually, in recent years we have observed the opposite, that is, the existence of etiological factors, which are part of medical illnesses or conditions that intrinsically relate to addiction and/or substances of abuse.

This new concept is currently known and internationally accepted as "dual diagnosis." Within this new conceptualization of substance abuse disorders and

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dual diagnosis, a series of factors are currently perceived as determinant conditions vis-à-vis substance abuse and dependence. Among these factors we need to include (1) genetic factors, (2) neurobiological factors, (3) psychological factors, (4) behavioral aspects, and (5) sociocultural components.

125.2 Comorbidity Issues

125.2.1 Determinants of Substance Abuse and Dependence

Within this context, we need to address the following factors:

125.2.1.1 Genetic Factors

In alcoholism, genetic factors have been found to play a big role based on family, twin and adoption studies (Nguyen et al. 2011). We must emphasize, however, that alcoholism has been found to also play a key role as a comorbidity factor in other psychiatric disorders, such as depression, bipolar disorder, antisocial personality disorder, conduct disorder, and attention deficit hyperactivity disorder. Attempts are also currently made to categorize alcoholism into clinical phenotypes or subgroups based on factors such as family history of alcohol dependence, age of onset of the disorder, clinical symptoms, and personality traits (Nguyen et al. 2011).

Similarly, attempts have also been made to associate genetic influences vis-à-vis the use and abuse of tobacco and other drug dependencies such as cocaine and other stimulants, opioids, and cannabis (Nguyen et al. 2011). These attempts are also based on family, twin, and adoption studies. In this context, the dopaminergic and the serotonergic systems have been implicated in tobacco dependence and nicotine increases in the central nervous system. The cytochrome P450 enzyme system has also been implicated in the metabolism of drugs and other xenobiotic agents. In this context, the majority of nicotine is metabolized by the CYP2A6 into cotinine (Nguyen et al. 2011). In general, twin studies have demonstrated that genetic factors play a big role in the transition from drug initial use and drug dependence. In some studies, it has also been found that personality variables such as "sensation seeking" play an important role in the prediction of both substance abuse and dependence.

With respect to cocaine and other stimulants, it has been advanced that personality traits such as impulsivity and novelty seeking, as well as an individual response to stress, may be a contributing factor to cocaine addiction (Nguyen et al. 2011). Opiates, including morphine and codeine are drugs that originate from opium; all opioids are composed of substances with morphine. Oral opioid abuse in the United States has increased from 2002 to 2004. It has been found no poor metabolizers in a sample of opioid – dependent cases, thus suggesting that CYP2D6 defective genotypes may provide pharmacogenetics protection against developing opioid dependence (Nguyen et al. 2011).

Cannabinoids such as marijuana is the most commonly used illicit drug in the United States, accounting for 75 % of all illicit drug use. Family studies have indicated that the use, abuse, and dependence of cannabis tend to aggregate in

families (Nguyen et al. 2011). It looks that there is a relationship between the use of cannabis and the development of nicotine dependence and also the subsequent use of hard drugs. There is also increased evidence that the endogenous cannabinoid system plays a major role in the brain's reward pathways. Obviously, genetic factors play a big role in the risk for development of substance use disorders.

The role of genetic factors underlying certain comorbid conditions has also been reported. Emerging evidence suggest overlapping vulnerabilities with common genetic factors predisposing individuals to both substance use and mental disorders or to increasing the risk of having a second disorder once the first appears. For example, variations in the catechol-*O*-methyltransferase gene regulating the enzyme that breaks down dopamine confer vulnerability for developing schizophrenia in adulthood for those who were exposed to cannabis in adolescence (Caspi et al. 2005). Common genetic risk has been reported for several co-occurring psychiatric disorders such as of major depression, nicotine dependence and conduct disorders and antisocial personality disorder (Fu et al. 2007), bipolar disorder and alcoholism (Yasseen et al. 2010), or alcohol dependence and comorbid drug dependence (Dick et al. 2007).

125.2.1.2 Neurobiological Factors

It has been clearly demonstrated that drug addiction is a relapsing disorder categorized by compulsive use of drugs, the inability to control drug intake, and its continued use despite associated negative consequences (Schmidt et al. 2011). The recent focus on the complex neurochemical, biochemical, and structural changes in the brain has shown an impact in the five major classes of drugs; they are as follows: psychostimulants, opiates, ethanol, cannabinoids, and nicotine. Despite the fact that different classes of abused drugs have different mechanisms of actions, there are major similarities among them insofar as the brain circuits modifications observed via repeated exposure to these drugs. The limbic nuclei, including the amygdala, hippocampus, and medial prefrontal cortex send major glutamatergic efferent projections to the nucleus accumbens. The reinforcing effects of all drugs of abuse and due to actions in the limbic system, a circuit of nuclei that is responsible for the influence of motivational, emotional, contextual, and affective information and behavior. Currently, there are overwhelming evidence that demonstrate that increased dopamine neurotransmission contributes to the reinforcing effects of psychostimulants, opiates, ethanol, cannabinoids, and nicotine.

Psychostimulants, despite its different mechanisms of action, increase extracellular levels of dopamine, serotonin, and norepinephrine in the nervous system. It looks, based on animal studies, that enhanced dopamine transmission in the nucleus accumbens is important for the initiation and maintenance of psychostimulants self-administration behavior. Although increased norepinephrine transmission may be involved in the discriminative stimulus effect of cocaine, it does not appear to play a significant role in cocaine reinforcement. Likewise, the role of serotonin vis-à-vis cocaine reinforcement remains unclear. With respect to glutamate, it looks that altered glutamate transmission contributes substantially to cocaine-induced neuronal and behavior plasticity.

Ethanol produces numerous excitatory and inhibitory neurotransmitter systems in the brain, which result in mood elevation, sedative, anxiolytic, and ataxic effects. Marijuana remains one of the most widely abused drugs in the United States. The psychoactive effects of marijuana include euphoria, enhanced sensory perception, increased appetite, analgesia, disrupted cognitive functioning, anxiety, paranoia, and at higher doses, sedation. Stimulation of nicotine acetylcholine receptors in the central nervous system is responsible for the diverse psychoactive effects of nicotine, including mood elevation, decrease anxiety, increased arousal, improved attentiveness, decreased appetite, muscle relation, and cognitive enhancement.

Similar brain regions, such as those involving stress, dopamine, and GABAergic and glutamatergic brain circuitries among others, are also involved in other psychiatric disorders including schizophrenia, mood disorders, or nicotine dependence (Volkow 2004; Moran et al. 2012).

125.2.1.3 Psychosocial Factors

While psychological and social factors can contribute to the development and maintenance of substance abuse and dependence across the lifespan for many individuals, it remains that other individuals often do not develop these disorders, even when facing similar circumstances and biologies (Shoptaw 2011). Once substance use disorders are established, accompanying neural changes and conditioned behaviors ascend in importance, with the roles of psychological and social factors having less impact in maintaining substance abuse or dependence.

Individuals with substance abuse or dependence often complain they have an "addictive personality." This popular term has, however, little empirical support; by contrast, research into long-standing psychological and personality "traits" shared by individuals with substance abuse or dependence shows a good deal of support for common characteristics, specifically: sensation seeking, delay discounting, and other components of impulsivity. In general, persons with antisocial personality disorder are two-and-one half times more likely than those without antisocial personality disorder to also meet the criteria for drug abuse and dependence after controlling for demographics characteristics and other psychiatric diagnoses. Also, individuals who met criteria for any personality disorder are 1.8 and 3.3 times more likely to be comorbid for drug abuse or drug dependence. Individuals with bipolar illness represent an important group who face genetic, neurobiologic, and environmental factors that can contribute to a high prevalence of comorbid substance abuse and dependence disorders. Epidemiological studies have repeated documented bipolar disorder with the highest rate of substance use disorders compared to any other axis I psychiatric disorder. They are more likely to have the mixed and rapid cycling subtype, which responds less to lithium therapy and has high rates of other comorbid psychiatric and medical disorders (Salloum et al. 2005, 2008).

Major depression is also a concomitant factor vis-à-vis alcohol and drug abuse and dependence. Actually, depressed individuals seek out substance use to mediate depressed feelings and thoughts. In general, persons in the general population who suffer from major depression, dysthymia, generalized anxiety disorder or panic disorder concurrent with problems drug use are more likely than those who do not

have these conditions to initiate and use prescribed opioids, presumably to minimize uncomfortable psychological states from those disorders. The presence of major depression with comorbid alcoholism and addictions is characterized by higher severity of symptoms (Salloum et al. 1995; Salloum and Jones 2008), with remarkably higher frequency of suicidal behavior compared to either major depression alone or alcoholism alone (Cornelius et al. 1995; Salloum et al. 1995). Depression and comorbid cocaine dependence has been noted to have high frequency of suicidal behavior and lethality symptoms (Salloum et al. 1996; Cornelius et al. 1998).

Individuals with schizophrenia have one of the highest rates of comorbidities with substance use disorders. Hallucinogens and stimulants can produce experiences similar to schizophrenia in nonpsychotic individuals. Anxiety disorders and substance abuse disorders co-occur at substantial rates. Links between posttraumatic stress disorders (PTSD) and substance abuse tend to be common. Impairments in inhibiting cognitive impulses are linked to using substances of abuse. Adult individuals with attention deficit hyperactivity disorder (ADHD) tend to also have substance use disorders. Among individuals with substance abuse and dependence, a large percentage of them also experience comorbid violence and aggression. Violence and aggression that occurs within the context of a close interpersonal relationship frequently co-occurs with abuse of alcohol or other drugs.

Childhood adversities, including parental substance abuse, family violence, physical sexual abuse, and poverty, have also been present among persons who suffer from substance abuse and dependence. Life stressors can also induce certain individuals to use tobacco, alcohol, or other drugs as a way of reducing psychological discomfort. It should also be noted that individuals who have strong social attachments to their families tend to suffer less from substance abuse or dependence.

125.2.1.4 Behavioral Factors

Much of human behavior is maintained and modifiable by its consequences through the process of operant conditioning; under this process, some consequences of behavior, called reinforces, increase the probability that a person will respect a behavior in the future. Reinforcement is deeply involved in shaping much of human behavior, from simple activities like walking and riding a bicycle to complex behaviors like writing, conversing, an extensive body of experimental research suggests that the external pattern of behavior that no call drug addiction, is also operant behavior that is maintained by its consequences (Silverman et al. 2011).

Early laboratory research in nonhuman subjects has provided strong evidence that drug addiction can be viewed as operant behavior maintained by drug reinforcement. Laboratory models of drug addiction in nonhumans provide a unique and rich service of information on the nature of drug addiction and the variables that affect it. Experimental studies in nonhumans and humans have also provided thorough analyses of the roles of basic elements of operant conditioning in drug self-administration. Reinforcement plays a major role in this regard; this has been demonstrated with cocaine, opiates, alcohol, benzodiazepines, nicotine, and marijuana among others. The role of "discriminative stimulus" is also a good example of certain environmental events that could lead to drug seeking and drug use.

In summary via laboratory and clinical research efforts we have strong evidence that drug addiction can be operant behavior that is maintained and modifiable by its consequences.

125.2.1.5 Sociocultural Factors

Mankind's relationship with substances served socially desired functions. Drugs were used as medicine, in the performance of rituals and religious functions, and as recreation. Sociocultural factors affect individuals either through several small group effects or through the larger social environment. Each of these factors and their implications may have both risk and protective properties; that is, they are part of the etiology as well as prevention and treatment of substance abuse and many psychiatric disorders. In this regard, during the last decade, the focus of research has moved from the investigation of a series of sociocultural factors in isolation to a study of their relevance and interdependence, as well as their links with genetic influences. In this context, society, culture, ethnicity, and race play a major role in the substance use and abuse, as well as their implications with respect to addiction at large in society (el-Guebaly and Ruiz 2011).

Social groups and the microenvironment effects may protect or facilitate an individual's drug use through one or several of social communities such as "the family unit and parenting," "peer group," "schools," "workplace," "social network systems and support," and "group identification and deviancy."

Larger social structures and/or macroenvironment can also play a protective role and/or facilitate drug use, among them neighborhood disorganization; adverse socioeconomic conditions; environmental availability via access, acquisition and distribution of drugs; cultural influences, acculturation process, and media; and/or worldwide electronic information. These previously mentioned sociocultural variables have significant implications in every aspect of the management of the spectrum of the substance use disorders; for instance, sociocultural variations may affect the meaningfulness of the diagnostic categories in the substance use disorders, and the importance of fully assessing an individual's psychosocial and environmental problem that may affect the diagnosis, treatment, and prognosis, via social preventive strategies that could help people to be inoculated against the social pressures precipitating drug trial and experimentation through social coalition building. Likewise, high-profile media campaigners against drug use and abuse; additionally, via prevention effects on a global scale such as the WHO Framework Convention on Tobacco Control"; also, through the use of social treatment strategies via family therapy, group therapy, network therapy, therapeutic community strategies, sober living homes, twelve step programs, employee assistance programs (EAPS), prison settings, as well as other treatment strategies directed to the treatment and prevention strategies.

125.2.1.6 Associated Medical Factors

Within the context of licit and illicit use of substances and drugs, we have to take into consideration the most common medical factors and/or associated conditions with this use and abuse of substances. Among them are the maternal and neonatal

complications of alcohol and other drugs (Kaltenbank and Jones 2011). The public's concern and the subsequent behavioral and medical research on the effects of prenatal exposure to substances is grounded in the concept that disturbances during the development in utero are a direct result if these substances altering the psychical and/or nervous systems of the child. Among the drugs considered capable of negatively impacting the children of abused mothers, we find alcohol, opioids, cocaine, amphetamines, inhalants, toluene, gasoline, marijuana, nicotine/tobacco, benzodiazepines, and hallucinogens, such as PCP.

These have also been excellent reports related to the medical complications resulting from drug use and dependence (Lee et al. 2011). In this context, the critical issue is to provide excellent care of drug users with medical conditions. Overlapping symptoms and syndromes, adherence to treatment, prevention of complications, the use of injection drug use, overdoses, sexual risk behavior, immunizations, and confluent risks and associated outcomes on drug addicts who also suffer from cardiovascular disease and/or cancer; alcoholic pancreatitis; liver disease and viral hepatitis; sexually transmitted diseases such as syphilis, gonorrhea and chlamydia, genital herpes, human papilloma virus, and trichomoniasis; skin and soft-tissue infections; infective endocarditis; tuberculosis; pneumonia; chronic lung disease; pulmonary complications of crack cocaine use, drug use, and neurologic disease; and other types of medical complications all play a major role in dealing with the medical complications of drug use and dependence (Lee et al. 2011).

Likewise, psychiatric complications of HIV-1 infection and drug abuse has led to 60 million drug abuser individuals having gotten infected with HIV-1 worldwide of which 42 million are still living with the infection (Goforth et al. 2011). The introduction of zidovudine (AZT) and later of the highly active antiretroviral therapy (HAART) has helped to decrease both the mortality and the incidence of AIDS (Goforth et al. 2011). Additionally, not only the type of psychiatric disorders related to HIV infection but also psychosocial issues such as abuse; risk-taking behavior; adherence to CART; and central nervous system involvement such as delirium, dementia, sleep disorders, psychosis and anxiety, as well as myopathies and pain with respect to the peripheral nervous systems involvement can all play a major role related to psychiatric complications of HIV-1 infection and drug abuse. Examples of neuropsychiatric infections and malignancies associated with HIV infections are atypical aseptic meningitis, cytomegalovirus (CMV) encephalitis, herpes simplex virus encephalitis, candidiasis, varicella zoster virus encephalitis, liposarcoma, and many others.

Acute and chronic pain should be considered a potentially serious illness in its own right. Chronic pain is associated with mood disturbances, sleep disorder, loss of function, impaired quality of life, and caregiver burden (Portenoy 2011). There is a complex relationship between pain management and the clinical issues surrounding the problems of drug abuse, addiction, and diversion. The key role played by opioid drugs, which are both essential medical treatments and a major source of abuse, has justified the exploration of this relationship. In this context, the implications of pain assessment, the framework for interpreting the nature of the pain, the

relationship between pain and substance abuse, including its terminology such as tolerance, physical dependence, addiction, and abuse, misuse, and other related terms are crucial to understand its relationship. Finally, interpreting nonadherence behaviors in the medical context, the principles of opioid therapy are all essential for a good success on this issue, especially when dealing with patients with history of previous substance abuse.

In the context of substance use disorders, it is very important that we take into consideration the potential existence of co-occurring psychiatric disorders (Dennison 2011). For instance, use of, and withdrawal from, alcohol and other substances of abuse can cause, mimic, or mask psychiatric symptoms. The overlap of these signs and symptoms makes it difficult to accurately diagnose all conditions present. Of course, failing to diagnose any co-occurring disorder (COD) increases the likelihood that the appropriate individual's treatment needs will not be met, thus worsening the patient's prognosis. For some time, individuals with both psychiatric and substance problems have been called "dually diagnosed"; given that dually diagnosed patient are very complex based on the conceptualization of the problem or illness, many professionals prefer to call them "COD" or having "co-occurring disorders."

The World Health Organization (WHO) reports that drug interactions are a major source of morbidity and mortality. Drug interaction can also occur with the coadministration of therapeutic medications with alcohol, with other prescriptions drugs, with illegal or illicit substances, or with other pharmacological interventions that are used in the treatment of substance use disorders. In this context, we need to be aware of the mechanisms for drug interactions. Also important is the understanding of drug interactions between opioids used for the treatment of opioid dependence and other medications, drug interactions between opioids and antiretroviral medications, and interactions between opioids and medications used to treat other infectious diseases such as hepatitis C with interferon, tuberculosis with rifampicin, and with antibiotics at large. It is also essential to be aware of drug interactions between opioids and benzodiazepines and, likewise, between opioid analgesics and other medications; between stimulants and other medications and between alcohol and other medications such as benzodiazepines, bupropion, methadone, cocaine, and methylphenidate; and finally, between cigarette smoke or nicotine and other medications (Haass-Koffler and McCance-Katz 2011).

Despite the fact that in the United States there is certain discomfort with the concept of "dual diagnosis" as previously alluded to (Dennison 2011), internationally, this is not the case. In Europe, primarily in Spain and Italy, as well as in Latin America, primarily in Argentina, Colombia, and Peru, this concept of "dual diagnosis" is not only well accepted and extensively used but expanding at full speed among countries and regions of the world (Roncero et al. 2011).

Within the context of this publication, we must also underline that ethnic, racial, and cultural groups also manifest their medical illnesses, including psychiatric illnesses, within the context of their culture, tradition, beliefs, and heritage (Lewis-Fernandez et al. 2011; Munoz et al. 2007).

125.3 Conclusion

Within the field of substance abuse, the concept of "comorbidity" has greatly expanded and is better understood from a clinical point of view in recent years. In this context, the topic of "dual pathology" is greatly expanded from an international viewpoint, particularly, in countries such as Spain, Italy, Argentina, Peru, Colombia, and others.

This now conceptualized "comorbidity" has also led the field of addiction to focus on a series of determinants of substance abuse and dependence. Among them, genetic factors, neurobiological factors, behavioral factors, socioeconomic factors, and associated medical factors. Within this context the conceptualization of "comorbidity" and/or "dual pathology" has both greatly advanced in the field of substance abuse/addiction. In this chapter, we have tried to enhance its medical/clinical roles; hopefully, further attention to this area of the addiction field will lead to a better understanding of addictive behaviors and also lead to better strategies in their treatment components.

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Section X

Special Populations

Giuseppe Carrà and Nady el-Guebaly

Special Populations: An Introduction

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Giuseppe Carrà and Nady el-Guebaly

Abstract

The challenge of this section is to select special populations with needs not otherwise covered by the rest of the textbook. The barriers encountered in the design of gender-specific programs, the special needs of seniors, LGBT-specific programs, the health of physicians, and increase in substance use in people displaced by conflicts across the world, and in those affected by disasters, all are addressed in the section. The section also highlights the international paucity of statistical data related to 96 special needs groups as compared to the available general population data.

A systematic research effort will be required.

The challenge of this section is to select special populations with needs not otherwise covered by the rest of the textbook. Six such groups are highlighted.

The first chapter addresses the special needs of women. We recognize the awkwardness of addressing half of humanity as a "special population," and indeed, a separate section can be devoted to women in future editions. Drs. Moran-Santa Maria and Brady present a masterful synopsis of the scientific endeavors focusing on women. Remaining gender disparities in research are acknowledged. The prevalence difference of various substance use disorders between men and women across the life cycle is outlined. These data for a number of African and Asian countries remain unavailable. This part of the chapter also addresses the increased exposure of female sex workers. While the "telescoping course" of

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females addicted to alcohol and the related biologic causes are well known, the chapter also addresses parallel reactivity to other drugs as well as areas for further study. The treatment section describes different responses to pharmacotherapy as well as the barrier encountered in the design of gender-specific programs and the parameters of improved outcome.

The second chapter describes the special needs of seniors, soon to become a quarter of humanity but with disproportionately higher service needs as compared to other age groups. Dr. Crome summarizes the available prevalence figures of older people with substance misuse in the United Kingdom and the United States. The related costs to a developed community are outlined. The chapter's middle section carefully details distinctive issues in substance use among the elderly and provides a window on the higher comorbid health conditions. This perspective leads to a thorough consideration of the issues central to the assessment of older people: the barriers to detection and the benefits and limitations of the available screening instruments in this population. A paucity of data addresses the disproportionate need for pharmacological and psychological treatments. Among clinical trials, there remains a lack of evidence about safety issues in this age group. There are few trials of psychological treatment despite the observation that older people may in fact do better than their younger counterparts. Effective ingredients of comprehensive service programs and models are becoming identified. The chapter aptly concludes with the significant need for training of a competent workforce.

The third chapter is the first one to address a smaller subgroup of the international community burdened by significant stigmatization, the LGBT group. This chapter reviews the empirical evidence focusing by necessity on the North American scene, due to the shortage of data from elsewhere. Despite the challenges encountered in epidemiological surveys, the consensus is that the prevalence for substance use disorders is higher than for the general population due to stressors related to social rejection and various forms of homophobia. Examples of particular significance are the impact on adolescents "coming out" and individuals, members of "double minorities." The bars and circuit parties and more recently the Internet become the social foci of an underground community. The second half of the chapter addresses treatment and other remedial measures including for which LGBT-specific programs may be required as well as the competencies needed from care providers. The developing world being comparatively more opened to the subgroups described, it is plausible to assume that the various challenges described are more severe in the developing world.

The fourth chapter focuses on the health of physicians with implications for other caregivers as a special group. The chapter by Drs. Braquehais, Casas, et al. is based on the experience of the Galatea clinic in Barcelona (▶ Chap. 130, "Addictions in Physicians: An Overview"). A review of the literature concerning prevalence, possible causes, and drugs of abuse in various medical careers on both sides of the Atlantic is presented. The Physician Health Programs have attracted attention in the field due to their demonstrated excellent outcomes. These programs have evolved from a culture of denial and unrealistic expectations in the medical community to the development of successful strategies aimed at protecting patients and helping the physician recover back to the practice of medicine. A table lists the

various approaches in North America, Europe, and Australia, and key factors for prevention and treatment of physicians with substance use disorders are identified including among others confidentiality, specialized staff training, group approaches, and lengthy monitored follow-up. The chapter concludes with a description of the respected PAIMM program in Barcelona and its extended activities across Spain. The target is the range of mental disorders and voluntary help-seeking is encouraged.

The last two chapters deal with populations not commonly covered in our textbooks, but appearing regularly in our global media. Dr. Ezard reports on the staggering 45 million people currently displaced by conflicts across the world, two-thirds of whom in a "protracted situation" of more than 5 years. Patterns of substance use reflect a combination of pre-displacement patterns, host population patterns, and substance availability. The experience of various displaced groups, and they are unfortunately many, is described. Particular risk factors include being male, older age, multiple traumatic episodes, and economic drivers. While experiences of interventions to reduce substance-related harm among refugees are limited, a harm reduction approach is recommended from thiamine provision for heavy alcohol users to more structural interventions including community mobilization, alternate income strategies, and equity-based initiatives. Quantitative evaluations may be difficult to conduct and qualitative ones may be more realistic with common end points such as violence prevention.

The final chapter is an overview of the impact of disasters particularly on youth. Following an inventory of the challenges arising from biases inherent to the unpredictability of the events, the results of well-designed US studies following Hurricane Katrina but also the 9/11 attack on the World Trade Center as well as bushfire in Australia are presented analyzing the relation between disaster exposure and substance use. Higher levels of objective and subjective disaster exposure are linked with greater psychological symptoms and increase in substance use. Of the young people experiencing distress, the majority recover within a year. Post-disaster interventions are described based on the phase of recovery, e.g., immediate aftermath, within a year and over a year. Little research so far addresses pathways leading to substance abuse/PTSD comorbidity among youth. Identified remedial programs involve some type of family treatment, an evaluation of mental health and substance treatment needs, and provision of environmental resources.

The section also highlights the international paucity of statistical data related to special needs groups as compared to the available general population data. A systematic research effort will be required.

Women and Addiction

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Megan M. Moran-Santa Maria and Kathleen T. Brady

Contents

Abstract

Over the last 20 years, awareness of the significance of gender differences in addiction has grown exponentially in the United States. However, international studies of gender differences in addiction are scant. Understanding gender

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differences in epidemiology, etiology, risk and protective factors, clinical presentation, psychiatric comorbidity, course of illness, and treatment outcomes of substance use disorders (SUDs), particularly in developing countries, is critical to the implementation of effective treatment and prevention strategies that address both sexual risk and drug use.

127.1 Introduction

The definition, prevalence, assessment, and management of addictive disorders are dramatically influenced by social, ethnic, and cultural contexts. This is particularly true for understanding addictive disorders in women. Women from various cultures maintain diverse roles in society which can lead to a variety of coping mechanisms and behavioral adaptations that influence the prevalence and presentation of mental health problems and substance use–related issues. In this chapter, we present an overview of substance use disorders (SUDs) in women with an emphasis on international issues including social and cultural influences. Studies specifically focused on gender-related international issues in SUDs are reviewed.

127.2 Overview of Epidemiology

In 1993, the United States Congress approved legislation mandating that the National Institutes of Health (NIH) ensures that women and members of minority groups are included in clinical research studies that are pertinent to their health, the purpose of the research, and all other conditions that may be designated as appropriate by the director of the NIH (U.S. Congress Public Law 103-43 1993). Since then, the number of published research reports examining multiple aspects of SUDs in women and gender differences in SUDs in the United States has risen tremendously. These studies have provided critical insights into the epidemiology, etiology, risk and protective factors, clinical presentation, psychiatric comorbidity, course of illness, and treatment outcomes of SUDs in women. While the number of international studies of SUDs among women is increasing, there are still significant gender disparities in our knowledge and understanding of SUDs at a global level.

127.2.1 United States

In 2011, approximately 20.6 million Americans 12 years of age or older met the Diagnostic Statistical Manual of Mental Disorder (DSM-IV) criteria for current substance/drug abuse or dependence (Mental Health Services Administration 2012a). The prevalence of SUDs in men (10.4 %) was significantly higher than for women (5.7 %). In addition, the prevalence of current illicit drug use among men (11.1 %) was significantly greater than the prevalence of illicit drug use in women (6.5 %). Compared with women, men were more likely to use

marijuana (9.3 vs. 4.9 %), cocaine (0.7 % vs. 0.4 %), prescription drugs (2.6 % vs. 2.2 %), and hallucinogens (0.5 % vs. 0.3 %). The prevalence of current alcohol (56.8 % vs. 47.1 %) and tobacco (32.3 % vs. 21.1 %) use was also higher in men than women. Of note, the gender differences in the prevalence of current tobacco use was consistent across all types of tobacco (cigarette, pipe, cigar, and smokeless).

A similar epidemiological study of adolescents (ages 12–17) found no gender differences in general prevalence of SUDs (6.9 % for males and females) (Mental Health Services Administration 2012b). In addition, no gender differences in the prevalence of current alcohol use (13.3 % for males and females) or cigarette smoking (8.2 % for males and 7.3 % for females) were reported. However, the prevalence of current illicit drug use among adolescent males (10.8 %) was greater than the prevalence in adolescent females (9.3 %). Adolescent males were more likely than females to be current marijuana users (9.0 % vs. 6.7 %). However, adolescent females were more likely than males to report nonmedical use of prescription pain relievers (2.6 % vs. 1.9 %) and psychotherapeutic drugs (3.2 % vs. 2.4 %).

Data from large-scale epidemiological studies demonstrate a relatively high prevalence of certain co-occurring psychiatric disorders among women with SUDs as compared to men. For example, alcohol-dependent women are more likely to suffer from mood disorders and have a higher prevalence of primary depression than alcohol-dependent men (Regier et al. 1990; Kessler et al. 1997; Helzer and Pryzbeck 1988; Schuckit 1983). Moreover, compared with treatment-seeking men, treatment-seeking women are more likely to have multiple comorbidities (i.e., three or more co-occurring diagnoses in addition to the substance use disorder) (Brady and Greenfield 2009). Eating disorders (EDs) are particularly common among women with SUDs (Gadalla and Piran 2007). A number of studies have found that over 50 % of women receiving treatment for a SUD have histories of physical and/or sexual abuse and a high percentage meet criteria for posttraumatic stress disorder (PTSD) (Greenfield et al. 2010; Brady et al. 2004). Moreover, the severity of childhood trauma has been associated with an increased risk for cocaine relapse in women but not in men (Hyman et al. 2008).

127.2.2 International Epidemiological Data

The United Nations Office on Drugs and Crime (UNODC) and the World Health Organization (WHO) have provided the most recent estimates of the prevalence of drug use and SUDs among men and women at a global level. Consistent with data from the United States, UNODC reported that the lifetime, 12-month, and past-month prevalence rates of cocaine, amphetamine, marijuana, and ecstasy use were greater among men than women. However, the prevalence of tranquillizer and sedative use among women exceeded that observed in men (United Nations Office on Drugs and Crime 2012). In Afghanistan, women were more than twice as likely as men to report daily use of tranquillizers (United Nations Office on Drugs and Crime 2009). In South America and Central America, the lifetime prevalence of tranquillizer and sedative use in women was nearly double the prevalence estimates

for men (6.6 % vs. 3.8 %). In Europe, the lifetime prevalence of tranquillizer and sedative use among women was 13 % compared with 7.9 % for men. These findings are consistent for both adult and adolescent populations (United Nations Office on Drugs and Crime 2012).

The WHO collected data from 147 countries (representing approximately 88 % of the global population) (World Health Organization 2010). Estimates were based on international disease classification systems such as the International Classification of Diseases (ICD) and the DSM-IV (Kehoe et al. 2007; Rehm et al. 2009). Among males age 15 years and older, the prevalence of alcohol use disorders was estimated to be highest in Eastern European countries, parts of Asia, and the Americas. Among females aged 15 and older, the highest prevalence rates of alcohol use disorders were found in Eastern European countries, regions of the Americas, and the Western Pacific. The estimated prevalence of alcohol use disorders was lowest among men and women living in African and Eastern Mediterranean countries. The highest prevalence rates of SUDs for both men and women were found in select regions of South, Central, and North America.

There are a number of limitations to the UNODC and WHO reports. Data from a number of African and Asian countries were unavailable and therefore not included in the UNODC report. Thus, gender differences in the prevalence of illicit drug use may be not be generalizable to African and Asian countries. In addition, these findings were based solely on data from countries for which gender-disaggregated data were available and thus may lead to an underestimation of SUDs among women at a global level.

Socioeconomic and cultural factors continue to be major challenges to accurate and reliable international assessments of SUDs among women. For example, in the United States, childhood sexual abuse is a strong predictor of SUDs in women (Boyd and Mackey 2000). Women living in socially conservative cultures may be reticent to disclose childhood sexual abuse with researchers. In addition, logistical challenges can prevent researchers from collecting data from women living in rural areas. Interpersonal violence and SUD data have often been collected in the emergency departments of urban hospitals and may not be generalizable to the entire population (Treno et al. 1998).

127.2.3 Substance Use in Sex Workers

One of the most consistent epidemiological findings is the high prevalence of substance use among female sex workers. Approximately 30 % of women who use injectable drugs (ID) work in the sex trade (El-Bassel et al. 2012; Poon et al. 2011). A high prevalence of cocaine and alcohol use was found in a study of female sex workers in South Africa (Wechsberg et al. 2006). In addition, a community-based survey of sex workers in India found that close to 100 % exhibited symptoms of alcohol dependence (Chakraborty et al. 1994). There is a strong reciprocal relationship between involvement in the sex trade and substance use. For example, sex workers are often from impoverished backgrounds so it is not

uncommon for them to use the sex trade as a means to support not only their own drug habit but also their partner's habit (Kumar and Sharma 2008). Female sex workers have a high risk of exposure to interpersonal violence and are often encumbered with economic challenges and childcare issues. Thus, substance use among female sex workers may be an attempt to self-medicate and alleviate stress and anxiety. Substance use reduces the likelihood of sex workers to engage in harm-reduction behaviors. In India, more than half (52 %) of female sex workers reported alcohol use prior to sex, and 38 % were less likely to use condoms after alcohol use (Kumar 2003). Female sex workers that use drugs have an elevated risk for HIV infection and other sexually transmitted diseases. In India, the prevalence of HIV infection among sex workers who use injectable drugs (IDs) was 16 %, which is nearly double the HIV prevalence estimate of 8.4 % for female sex workers. Studies have found that HIV infection among women who use IDs is escalating (Bridge et al. 2010; El-Bassel et al. 2010). In fact, a meta-analysis of drug use across 14 countries found that women who use IDs have a significantly greater risk for HIV infection than males that use IDs (Des Jarlais et al. 2012). Despite these data, few if any studies have employed a systematic approach to IDs use among women at a global level, and countries with the highest prevalence of HIV often fail to provide gender-disaggregated data. Moreover, underestimates of the prevalence SUDs among women in developing countries could undermine the implementation of effective prevention strategies addressing both sexual risk and drug use.

127.3 Gender Differences in Course of Illness

One of the most consistent findings in studies focused on gender differences in SUDs is the increased vulnerability of women to adverse medical and psychosocial consequences of addiction (Chatham et al. 1999; Gentilello et al. 2000; Henskens et al. 2005; Hernandez-Avila et al. 2004; Mann et al. 2005). Women advance more rapidly than men from initial to regular use and to the first treatment episode. Despite fewer years and smaller quantities of use at treatment entry, substance use severity is generally equivalent in men and women, and women average significantly more medical, psychiatric, and adverse social consequences from substance use (Hernandez-Avila et al. 2004; Mann et al. 2005; Randall et al. 1999). This has been called the "telescoping" of SUDs in women, and differences in biology as well as psychosocial factors contribute to this phenomenon.

127.4 Gender Differences in Biology and Pharmacotherapy

127.4.1 Biological Influences

Important gender differences exist in the physiologic effects of alcohol. Women have higher blood-alcohol concentration after drinking equivalent amounts of alcohol as compared to men. This is primarily because women have a lower

percentage of total body water (Marshall et al. 1983) and a lower concentration of gastric alcohol dehydrogenase, the primary enzyme responsible for the metabolism of alcohol (Frezza et al. 1990). These gender differences contribute to higher blood-alcohol concentrations in women which provide a biological basis for the heightened vulnerability to psychological and medical consequences of alcohol consumption in women. Women develop alcoholic liver disease after comparatively shorter and less-intense drinking as compared to men, and neuroimaging studies suggest increased sensitivity to alcohol-induced brain atrophy in women as compared to men (Mann et al. 2005; Fuchs et al. 1995; Hommer et al. 1996).

There is less data available concerning gender differences in physiologic effects and medical consequences of other drugs of abuse. Women generally metabolize nicotine more slowly than men (Benowitz and Hatsukami 1998). Some studies suggest that men are more sensitive to the rewarding effects of nicotine than women (Perkins et al. 2000). In addition, negative affect regulation may be a stronger motivation for nicotine use in women (Hogle and Curtin 2006; McGee and Williams 2006). Both animal studies and human laboratory data indicate that females are more sensitive to the subjective effects of stimulants (Kosten et al. 1996; Roth and Carroll 2004a, b). Of interest, cocaine-dependent women experience fewer cerebral perfusion defects (Levin et al. 1994) and less frontal cortical neuronal loss (Chang et al. 1999) compared to men with comparable drug use histories, findings that could be related to gender differences in cocaine-induced cerebral vasoconstriction (Kaufman et al. 2001). There have been many gender differences observed in the pharmacologic properties of opiates, including analgesic effects, but gender differences in abuse potential have not been systematically studied in humans. However, animal studies suggest that mu agonists may be reinforcing to females over a broader dose range, and females self-administer greater quantities of opiates as compared to males (Cicero et al. 2000, 2003).

Accumulating evidence from preclinical and clinical studies indicate that hormonal changes associated with the menstrual cycle may impact both craving and the behavioral responses to drugs. For example, estrogen augments behavioral responses to cocaine in female rats by modulating the mesocorticolimbic dopamine system (Lynch et al. 2002; Perrotti et al. 2001; Russo et al. 2003). In humans, this may explain reports of increased responsiveness to cocaine cues and higher quantities of use in women presenting for treatment (Robbins et al. 1999; Kosten et al. 1993). In one study, women reported less pleasurable effects of cocaine during the luteal phase, compared to women in the follicular phase and men (Sofuoglu et al. 1999). As such, women may be more vulnerable to relapse during the follicular phase, when progesterone levels are lower, compared with the luteal phase (Wilcox and Brizendine 2006). In another study, administration of progesterone to women during the follicular phase attenuated the positive subjective effects of cocaine (Evans and Foltin 2006). This is an area of active investigation which could have important implications for treatment.

Neuroimaging studies have also provided important information about the neural processes underlying sex differences in SUDs. During a stress task, female cocaine users showed greater left frontolimbic brain activation than males (Li et al. 2005).

Using positron emission tomography (PET) during cue-induced cocaine craving, Kilts and colleagues found greater activation in women in the dorsal striatum and anterior cingulate cortices and lower activity in the amygdala, which assesses the pleasure of an experience and connects it with its consequences (Kilts et al. 2004). In a recent exploration of sex differences in neurocognitive and brain responses to emotions, stress, and drug-related cues, Potenza and colleagues found that women had greater reactivity to stress-related cues and men showed higher responses to drug cues (Potenza et al. 2012).

Gender differences in the physiologic and subjective effects and medical consequences of opiates, marijuana, and other drugs of abuse are vastly under explored. Considering the important gender differences that have surfaced with careful investigation in the areas of alcohol, nicotine, and cocaine dependence to date, this is clearly an area that warrants attention in future studies and could have major implications for gender-sensitive prevention and treatment efforts.

127.4.2 Pharmacotherapy

The findings concerning gender differences in the neurobiology of substance use disorders and the potential impact of hormones on the subjective effects of substances of abuse and relapse suggest that there may be gender differences in the most efficacious approach to pharmacotherapeutic treatment. Findings from animal studies also indicate important gender differences in response to the medications that can be used to treat addictions. Campbell and colleagues reported that baclofen-treated female rats were less likely to acquire cocaine self-administration as compared to baclofen-treated male rats (Campbell et al. 2002). In another study, ketoconazole was found to decrease opiate self-administration more in female as compared to male rats (Carroll et al. 2001). However, there has been little clinical research exploring gender differences in response to agents currently used in the treatment of substance use disorders. Based on animal research studies demonstrating that progesterone decreases response to stimulants, Evans and Foltin explored the impact of exogenous progesterone on smoked cocaine and found an attenuation of the positive subjective effects of cocaine in women, but not in men (Evans and Foltin 2006). This is clearly an area which warrants further gender-specific investigation.

As detailed above, substance-dependent women are more likely to suffer from mood and anxiety disorders and to be victims of physical and sexual abuse as compared to men. As such, medication treatment of comorbid conditions is likely to be particularly important in the treatment of substance-dependent women. In this regard, one study comparing an SRI (sertraline) to a tricyclic antidepressant (imipramine) in the treatment of depression found that premenopausal women had a preferential response to sertraline (Kornstein et al. 2000). A recent study exploring treatment with a combination of sertraline and naltrexone in individuals with alcohol dependence and major depression found significantly improved alcohol-related and depression outcomes in the combination treatment group (Pettinati et al. 2010).

As such, while the evidence does not support the use of antidepressant medications in the absence of depression in substance-dependent individuals, careful evaluation of depression and psychiatric disorders and appropriate treatment will likely improve treatment outcomes. Other studies have provided preliminary evidence that bupropion, a pharmacologic agent with FDA approval for both the treatment of depression and smoking cessation, may be more efficacious in women as compared to men (Perkins et al. 2000).

127.5 Treatment

Although women are generally underrepresented in substance abuse treatment programs, retention and relapse rates for women are comparable to men (Greenfield et al. 2007; Hser et al. 2001; Mangrum et al. 2006). Data from several studies suggest that women exhibit more favorable treatment outcomes than men. For example, studies have demonstrated that women have shorter relapse periods and a higher incidence of abstinence at 6 months (79.3 % women vs. 54 % men) and 5 years (odd ratio = 1.9) following treatment (Henskens et al. 2005; Dawson et al. 2005; McKay et al. 1996; Moos et al. 2006). In addition, women have a greater improvement in physical health and are more likely than men to seek support after a relapse episode (McKay et al. 1996; Hser et al. 2005; Project Match Research Group 1997).

127.5.1 Gender-Specific Treatment Programs

Arguments in favor of gender-specific treatment include differences in interaction styles and men's traditional societal dominance, which might negatively affect women in mixed-gender programs. Moreover, women and men with SUDs differ significantly in terms of risk factors, co-occurring psychiatric conditions, motivations for treatment, and risks for relapse. Gender-sensitive treatments can address these issues directly and may improve treatment seeking, retention rates, and treatment satisfaction. However, data from studies examining effectiveness of gender-specific treatment programs for women are mixed (Greenfield et al. 2007; Ashley et al. 2003; Copeland et al. 1993; Niv and Hser 2007). For example, residential programs that allow children to accompany their mothers have higher retention rates (Hughes et al. 1995; Szuster et al. 1996). In addition, women enrolled in women-focused outpatient or residential treatments have higher completion rates than women enrolled in standard substance abuse treatment programs (Brady and Ashley 2005; Dahlgren and Willander 1989). Although other studies have found that women-only programs provide similar treatment outcomes as mixed-gender programs, these studies have noted that socioeconomic status, addiction severity, and comorbid psychiatric diagnoses are significant factors in determining the effectiveness of women's treatment programs (Greenfield et al. 2007; Niv and Hser 2007).

Prevention strategies and treatment programs for women must incorporate the culture and diversity of each region. For example, in India, the UNODC has distributed guidebooks outlining prevention strategies to women's groups, health-care providers, legislators, and the public and also sponsored nongovernment pilot programs aimed at prevention strategies particularly for women at risk for the development of SUDs (United Nations Office on Drugs and Crime 2004). In other regions of the country that have a high population of female sex workers and women who are considered "social outcasts," funding has been provided for a SUD treatment center for women that employs peer educators who are often HIV positive and have a history of a SUD (United Nations Office on Drugs and Crime 2004). A general lack of awareness of the prevalence of SUDs in women may interfere with the development of gender-sensitive prevention and treatment efforts in some countries. Thus, identifying ways to include women in epidemiological studies of SUDs may be the first step in garnering support for gender-sensitive treatment programs. In addition, education of treatment providers about gender differences in the etiology of SUDs may help overcome the attitude that women do not require specialized treatment options. It is also critical that standards and guidelines for treatment include measures that protect the confidentiality of victims of domestic violence, restore relationships with family and community members, and use a nonconfrontational approach to therapy. Treatment programs, whether mixed gender or women only, that pay special attention to psychiatric comorbidity, family and parenting issues, victimization, and gender-specific barriers to treatment are likely to be more successful for women.

127.5.2 Gender-Specific Barriers to Treatment

In the United States, women are less likely than men to enter treatment programs (Greenfield et al. 2007). Consistent with this finding, studies from countries that have collected gender-specific data demonstrate that women are consistently underrepresented in SUD treatment programs. For example, in Europe, the ratio of men to women in treatment for marijuana, cocaine, and amphetamine use is 4:1, which is significantly higher than the gender ratio of use for these substances (United Nations Office on Drugs and Crime 2012). Across substance use treatment centers in India, only 3 % of the 16,942 new patients were women. Men represent approximately 76–90 % of patients enrolled in substance use treatment programs across South Africa (Wechsberg et al. 2006; United Nations Office on Drugs and Crime 2002).

Globally, women with SUDs have less access treatment programs and harm reductions services than men with SUDs. For example, although 10 % of all substance users in Afghanistan have access to treatment, only 4 % of female drug users have access to treatment (United Nations Office on Drugs and Crime 2009). In eastern European countries, budgetary constraints and bureaucratic challenges have excluded incarcerated women from antiretroviral and opioid replacement treatments but have not excluded incarcerated men (Fair 2009; Pinkham et al. 2012).

Globally, there are a limited number of gender-based treatment programs. This is particular challenge for women who have been exposed to domestic violence, who may be more reluctant to attend group treatment programs that include men. In addition, there are few treatment programs for individuals with comorbid substance use and psychiatric disorders.

Sociocultural factors (e.g., shame, lack of spousal/family support) can also be significant barriers to women seeking treatment for SUDs. The social stigma attached to substance use in societies that value traditional roles for women as domestic caregivers can prevent women from seeking treatment. Women who drink alone may transition to alcohol dependence without their family's knowledge. In fact, one study found that in South Korea, women sought treatment only after the physical symptoms of drug withdrawal appeared (Lee and Kim 2000). In addition, women living in culturally conservative societies may not feel comfortable discussing sexual abuse and/or may not be knowledgeable of their own family history of SUDs. Relationship dynamics can also impact women's decision to seek treatment for SUDs. Women may be more reluctant to leave home for long-term treatment out of fear that separation from the family will lead to divorce and threaten family stability (Haj-Yahia 2000). In addition, women who are exposed to domestic violence exhibit self-destructive behaviors and are more reliant on their partners and thus less likely to engage in treatment and harm-reduction strategies (El-Bassel et al. 2000; Frye et al. 2001).

127.5.3 Special Issues: Pregnancy

Although global awareness of the adverse consequences associated with maternal substance use during pregnancy has increased, drug use during pregnancy remains a significant problem. For example, in the United States and Canada, 32 % of the 863 pregnant women who were surveyed reported occasional alcohol use, 16 % reported regular alcohol use, and 11 % reported heavy alcohol use (Edwards and Werler 2006). In utero exposure to alcohol is associated with fetal alcohol syndrome (FAS), characterized by irreversible neurological damage, developmental delay, facial malformations, and behavioral problems (Manning and Hoyme 2007). Another study of 1,632 mothers, 25 % reported using tobacco, 23 % alcohol, 6 % marijuana, and 1 % barbiturates during pregnancy (Arria et al. 2006). Screening for substance use in primary health-care and obstetric clinics is problematic since pregnant women face social stigma and legal problems which may prevent them from discussing substance use habits with health-care providers. In some countries, legislation and health-care policies are significant treatment barriers for pregnant women with SUDs. In the United States, laws that criminalize drug use during pregnancy in some states can prevent pregnant women from speaking openly with clinical care providers about their substance use (Paltrow 1999). In Russia and Ukraine, pregnant women with SUDs risk forced abortion and termination of parental rights (Eurasian Harm Reduction 2012; Canadian HIV/AIDS Legal Network and E.V.A 2012).

Pregnant women seeking substance abuse treatment often have additional health problems including HIV and other STDs, as well as psychiatric problems and abusive living situations. Thus, routine screening for trauma, victimization, and depression for this at-risk population is necessary (Tuten et al. 2004; Velez et al. 2006). A multidisciplinary approach to treatment that provides state-of-the-art treatment for SUDs integrated with psychosocial support and psychiatric, medical, prenatal, and gynecological care has been implemented in a number of countries, including Austria, Canada, the Czech Republic, and India (United Nations Office on Drugs and Crime 2004).

127.6 Conclusion

International research clearly indicates that gender-sensitive substance use policies and programs cannot ignore cultural influences. Large cross-national variation in gender differences in substance use disorders makes it clear that biological factors alone do not account for gender differences in substance use and addictions. Policies, education, and prevention and treatment efforts must take into account both the biological differences and the culturally defined gender roles that specify expected and tolerated drug use behavior in men and women. Cross-national research can help to explicate the complex interactions between biology, individual-level, and societal-level variables that influence alcohol consumption and drug use and allow us to design better-targeted prevention and intervention efforts for both genders worldwide.

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Older People and Substance Misuse

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Ilana B. Crome

Contents

Abstract

This chapter will outline the scale of the problem of substance misuse in older people, the burden of disease it incurs, morbidity and mortality, societal costs, and financial liability. Predictions are that over the next 20 years, there will be both an increase in the proportion of older people in the population and that older people will be using more alcohol, illicit substances, and prescription drug use compared with the past two decades. The nature and extent, the predictors and preventive potential, and the adaptations of successful treatment interventions will be outlined. Evidence is provided to demonstrate that the

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detection, intervention, and development of care models that are likely to improve the health and well-being of older people with substance misuse should be instituted. This is an area of utmost relevance to all clinicians: old age psychiatrists, addiction specialists, geriatricians, nurses, psychologists, social workers, and their teams. Researchers in gerontology, sociology, and economics, as well as policy makers and commissioners, are likely to find the implications and gaps of interest.

128.1 Introduction

This topic is important because of the scale of the problem, the burden of disease it incurs, morbidity and mortality, societal costs, and financial liability (Crome et al. 2011). In the UK, people over the age of 65 years constitute approximately 18 % of the UK population: the prediction is that by 2020, this will rise to 25 %. This increase in the proportion of older people is reflected in other countries (Han et al. 2009; EMCDDA 2009).

There is accumulating evidence that older people are using more alcohol, illicit substances, and prescription drug use, over the past two decades. National surveys of alcohol, illicit drugs, presentations to accident and emergency units, presentations to specialist services, and hospital admissions for poisoning and drug- and alcohol-related mental and physical disorders demonstrate this upturn. The prediction in the USA and Europe is that this is likely to double in the next two decades both because of the expansion in the number of older people and the rise in substance use by older people. At present, in the UK, it is estimated that 13 % of men and 12 % of women still smoke cigarettes (Seymour and Booth 2010). Indeed, smoking-related disorders are still the largest cause of premature death (Department of Health 2006). Older people receive most prescriptions dispensed by NHS: 45 % of prescriptions dispensed by the NHS are for the over 65s. These are often as multiple medications and it is estimated that 1/10 receive at least one potentially inappropriate drug, though it can be even higher (Chrischilles et al. 1990; Gottlieb 2004; De Wilde et al. 2007; Culberson and Ziska 2008). Psychoactive medications with abuse potential are being used by one in four older people (Simoni and Yang 2006), which is four times greater in women especially those who are widowed, less educated, lower income, poor mental and physical health, and socially isolated. In the USA 60 % of patients attending Accident and Emergency Departments with adverse drug reactions are over the age of 65 years, 25 % of which are psychotropic medications (IOM 2012).

In the UK alcohol consumption above the "safe recommended" limits (for adults) occurs in 20 % of men and 10 % of women over the age of 65. In one decade, there has been a 25 % rise in the proportion of older men and a 300 % rise in the proportion of older women drinking above the recommended daily limits of alcohol (The Health and Social Care Centre 2011). Mortality due to alcohol-related causes has proliferated in parallel with the surge in alcohol consumption. However, the greatest increase in the death rate due to alcohol-related problems is to be found

in those aged 55–74. Furthermore, although presentations to specialist drug services have shown a decline in younger age groups, there is evidence that there is a growth in new presentations to specialist drug services the over 40-year-olds.

Seventeen percent of patients in drug treatment units are over 40 years old (Benyon et al. 2007; Crome et al. 2009; NTA 2010). This is consistent with national surveys which indicate that 5 % of over 45-year-olds used an illicit drug in the previous year and 0.7 % used a Class A drug. Thus, illicit drug use can no longer be considered a "young man's disease." It is estimated that in the USA, 14–20 % of older people have mental health and substance misuse problems (Crane 1998; Oslin et al. 1998; Byrne et al. 1999; Crane and Warnes 2001; Brennan et al. 2003; Moore et al. 2003; Whelan 2003; Blazer 2009; Okura et al. 2010; IOM 2012).

These statistics are of concern as tobacco, alcohol, and illicit drugs constitute the 2nd, 3rd, and 8th leading risk factors contributing to the European disease burden.

There are considerable methodological issues that have to be considered. The age range for older adults can range from 40 to >90 years old. As described above, for drug treatment services, 40 years old is in the higher age range (Sidhu et al. 2012). National surveys often do not include over 60- or 65-year-olds, and, if they do, may not break down those over 60 or 65 into separate cohorts, e.g., 65–69- and 70–74-year-olds. Community-based studies may miss out the heavier drinkers or substance misusers because they do not include those in residential and nursing homes (Blazer and Wu 2009). In the USA, for example, evidence suggests that 25 % of nursing home residents are prescribed a benzodiazepine, with 10 % misusing the drug through lack of vigilance over the potential for long-term dependence (Svarstad and Mount 2005). Older people may suffer serious harm from substance use without being dependent, and indeed the criteria for dependence, which were developed in the adult population, may not be appropriate, valid, and useful for research or clinical purposes. Measurement needs to be relevant and reliable and includes all substances, i.e., alcohol, tobacco, prescribed medications, over-the-counter medications, as well as illicit drugs.

128.2 Costs

The costs of addictive substances to the community are astronomical. The latest estimates which are conservative reveal that alcohol costs the UK approximately £21 billion per annum, of which £2.7 million are health costs, £7 million are crime related, and £6.4 billion are costs in the workplace. Drug-related costs are reported to be £15 million with the costs to the NHS being £0.5 billion, but drug-related deaths are estimated at £1 billion. Ninety percent of the costs are due to crime. Moreover, the wider costs to family, friends, and communities are not quantified (National Audit Office 2008).

There are some specific data on older people (National Information Centre 2011). Older people incur greater costs than younger people. In 2010/2011 the cost of alcohol-related inpatient admissions in England for 55–74-year-olds was more than ten times that for 16–24-year-old age group at £825.6 million compared

with £63.8 million. Eight times as many 55–74-year-olds were admitted as inpatients compared with 16–24-year-olds, i.e., 454,317 with 54,682. In addition, the costs of alcohol-related inpatient admission were £1,994 million or over three times greater than the costs of A&E admissions at £636 million. The cost of admission of older men (£1,278 million) is calculated at almost double that for older women (£715 million).

In short, older people, especially older men, are more costly due to the magnitude and type of admission.

128.3 Distinctive Issues in Older People

There are many myths about older people and about people who have substance problems. The main aim is to attempt to destigmatize and to demystify attitudes to older people with substance problems. With an enriched understanding of the nature and impact of substance problems on older people, this becomes more achievable. However, there has been sufficient knowledge to date which could reasonably drive appropriate management. Even if an older person continues to use substances in exactly the same way they did as an adult, the impact may differ (Crome and Bloor 2005a, b; Crome et al. 2012).

Elderly people take what is readily available (Crome 1984). Older people may mistake tablets for sweets and may also use household products or denture cleaners which may be caustic. Older people have intensified risks for the development of chronic complex physical and mental health problems (Brower et al. 1994). This, compounded with physiological changes intrinsic to the ageing process, makes them more vulnerable to the effects of substances. So, despite the fact that substance use decreases with age, substance use is more dangerous. Older people are more likely to suffer adverse physical effects as substances accumulate due to decreased metabolism. Brain sensitivity to substances may be increased, thus amplifying the consequences of substance use. Older people are prescribed more drugs and are prescribed multiple medications so drug interactions are more likely than in their younger counter parts. Older people may present with somatic symptoms, which may not be attributed to the substance problem, and which may precipitate inappropriate prescription, leading to overdose. Furthermore, acute and toxic confusional states are common and may lead to a muddle over medication. Older people may not comply with medical instructions so that their treatment may not be optimal: they may either take too little or too much, the latter leading to overdose. Older people often take analgesics, sedatives, and hypnotics – all medications with addictive potential – for insomnia, anxiety, and pain. They may not be aware of the complications of taking such medications in themselves, but of the interaction when taken in combination with other prescribed or over-the-counter medications. Medication for substance use and mental health problems may worsen physical health, and medication for physical health may worsen mental health and substance use. Cognitive and functional impairment may be attributed to "ageing" rather than substance use. There is also scope for mistakes due to cognitive

difficulties. Poor recall may result in practitioners not being informed of the medications and other substances patients are taking, and not probing any further. Thus, it may not be obvious that a patient has taken an "overdose," and the presence of physical disease may confuse the picture, and drug use can resemble the physical problems of old age. This does lead to tricky, even unsafe, situations.

128.4 Lifespan Perspective

We now know that addiction can be a lifelong problem (Schutte et al. 2003; Hser et al. 2001; Jacob et al. 2009). It is estimated that about one in ten people with addiction problems begins misusing substances before the age of 19. Traditionally, two trajectories have been identified: older people who have had a lifelong history of substance problems or those in whom problems began in their later years. The original "geriatric giants," iatrogenesis, immobility, intellectual deterioration, incontinence, and instability, can be generated by substance misuse in the older person since substances affect virtually every organ (BGS 2006, 2007; Mehta et al. 2006; Gupta and Warner 2008; Moos et al. 2009). Older people may not need to use excessive amounts – especially if substances are combined – to suffer adverse effects. Delirium and dementia are common as is depression, anxiety, adjustment reactions, complicated grief, bipolar affective disorder, post-traumatic stress disorder, schizophrenia, and personality disorder may present differently in the older person, but it is beyond the scope of this chapter. Suicidal plans and attempts should be elicited. Other features that may include neglect and squalor, hoarding, and fear of falling are some indicators of risk of substance misuse. Falls are the most common health risk for older people who are misusing alcohol due to the impact on muscle tone and balance, and to osteoporosis, which may lead to fractures.

Alcohol may interact with many of the drugs prescribed to older people, e.g., antihistamines, acid-lowering drugs, antiepileptic medications, and antibiotics.

A study of primary care attendees in the USA has drawn attention further to the level of complications related to alcohol use (Moore et al. 2011). They suffered from hypertension (30 %), depression (12 %), gout (8 %), diabetes (5 %), ulcer disease (4 %), liver condition (4 %), and pancreatitis (1 %). Sleeping problems were present in nearly 40 %, gastrointestinal symptoms in 24 %, memory problems in 23 %, feeling sad or blue in 17 %, and tripping and falling in 18 %. Medication prescription further highlighted the potential for mistakes and interactions: 32 % were on antihypertensives, 18 % on ulcer medications, 18 % on nonsteroidal anti-inflammatory drugs, 17 % on antiplatelet medications, 13 % on nonprescription drugs, 12 % on antidepressants, 10 % on sedatives, and 7 % on opioids.

In a study on health conditions among ageing heroin addicts (Hser et al. 2001), 108 survivors were followed up for 33 years. The mean age was 58.4 years and they had used heroin for 29.4 years. Their current use of other drugs was unsurprising: 84 % were smoking cigarettes, 18 % drank alcohol daily, 23 % were using heroin, 21 % were using marijuana, 11 % were using cocaine, and 6 % were using

amphetamines. As with the alcohol cohort described above, there were high levels of comorbidity: 51 % were hypertensive, 50 % were overweight, 50 % had abnormal liver function, 22 % had hyperlipidemia, 33 % had abnormal pulmonary function, and 13 % had elevated blood glucose. They also tested positive for hepatitis C (94 %), hepatitis B (86 %), TB (27 %), and syphilis (4 %). These were considered to be conservative estimates (Cainelli 2008).

128.5 Assessment

The assessment should cover mental and physical state, capabilities, and current support.

Treatment of substance misusers begins with the style of assessment. There are several overarching principles. Though self-evident, unfortunately there is a need to emphasize the importance of providing high-quality treatment to this group of patients because this is too often neglected. This means that compassion, dignity, integrity, and equality with treatment for physical health should inform the manner in which patients are assessed in the first instance. This group has many features that may make them feel especially undervalued, undermined, and with low self-esteem. Health, life circumstances, behavior, status, and personal qualities may all be threatened: being older, in poor mental and physical health, impoverished, in family conflict, socially isolated, involved in criminal activities, with cognitive dysfunction and impaired functional life skills, and perhaps even being an immigrant, a victim of abuse, or a refugee. It is essential that the practitioner should be nonjudgmental and non-confrontational as that is more likely to catalyze rapport and cooperation with the patient, family, carers, and other staff for the assessment and for the implementation of the management plan.

The details of core components in the assessment of substance misuse have been covered elsewhere in the book, but it is worth mentioning that some issues are central to the assessment of older people. As has been mentioned, the presenting problem could well mask the substance use. Substances can cause the complications directly or indirectly by aggravating age-related impairment. A forensic history of public order and acquisitive offenses may shed light on the background. These mainly revolve around social factors which may be pivotal in terms of information gathering and future management. Consent and capacity need assessment in the first instance. Social vulnerability, e.g., isolation, risk of falls, and financial abuse are not uncommon. Social function assessed by activities of daily living and the support by statutory, voluntary, and private care as well as informal social support from family, carers, and friends are essential for formulating the problems. Social pressures arising from substance-using "carers," open drug dealing, and debt are fundamental to appraisal. Ethnicity may inform some of the social behaviors described above.

Any change in pattern of sleep, appetite, and mood should be elicited. A structured approach to the past medical and psychiatric history including impact on occupational and social function, as well as response to treatment, is mandatory.

Details about the substance misuse in the patient and family history of substance misuse may provide pointers.

The social environment of the older person is a key consideration. This is directly relevant to the assessment of the substance problem and medical manifestations, but it has an important bearing on the management plan. Removal of substances of abuse from the home is vital.

A recent study in the USA (Lin et al. 2011) has reported on community-dwelling older adults with mental illness or substance use disorder. Older adults with substance abuse and mental illness had significantly greater risk of having a chronic physical illness ranging from 1.2 for hypertension to 9.9 for dementia. The risk of having a diagnosis of chronic obstructive pulmonary disease, hip or pelvic fracture, or dementia in community-dwelling older adults with co-occurring mental illness and substance use disorder was 1.7–2.8 times as high as in those with mental illness alone. Since when these disorders co-occurred substantially, greater medical comorbidity was found, indicating the need for integration of medical facilities with mental health and substance abuse.

128.6 Barriers to Detection

There are a multitude of explanations as to why older substance misusers are not identified.

Lack of training, too little time, and therapeutic nihilism are some of the factors mitigating against the identification and treatment of substance problems in older people. These barriers can be overcome. Training is a key consideration because if implemented systematically it does give the opportunity to change negative attitudes through improving knowledge and enhancing skills. The UK has embarked on the implementation of a national undergraduate curriculum, and postgraduate training is also being tackled jointly by the Royal Medical Colleges (RCPsych 2012; ICDP 2007). Thus, medical practitioners will become competent in the assessment and management of substance issue.

Substance problems will be regarded as a medical matter. Like any other medical problems, learning how to take a detailed history and having a high index of suspicion will ensure that underreporting of symptoms, misattribution of signs, and increased awareness of subtle presentations in older people will be properly diagnosed. Ageism further legitimizes stereotyping of older people and hinders achieving suitable treatment choices. Training is an essential component in defying stigma particularly in this age group.

Awareness of the nature, extent, risks, and complications is necessary to detect the contribution of the presenting problems to the clinical picture. The practitioner should have a protocol of items and issues relating to ascertaining when any problems may be substance related. Substance problems are protean in presentation and therefore may well mimic almost any physical or psychiatric illness. In the

older person, though, this may be atypical, and could easily be missed, it a systematic approach is not applied by the professional.

In general, any alteration or a change to erratic uncharacteristic behavior or development of symptoms can be a warning sign. Poor response to treatment for medical or psychiatric illness; requests for prescription drugs; evidence of storing or sharing medications; a past family or personal history of substance misuse; a legacy of personal, social, occupational deficits; and perhaps involvement in criminal activities can serve to alert the practitioner. Unexplained falls, changes in eating habits, weight loss, irritability, and agitation are some of the features.

However, there are very specific questions that need to be covered and in some detail. Clarification should be sought from family, carers, colleagues, other professionals, and of course the patients themselves. Meticulous assessment of all substances used over the lifetime, within the last month and week, will do much to provide a picture of the pattern of use including the impact on physical, mental, and social functioning. The need for treatment, the type of treatment, and its success are important features.

Although there are a host of instruments which can support the assessment, there is no one tool that is standardized for older substance misusers and which can detect how the presentation may relate to substance use.

Use of AUDIT or AUDIT-C (a shorter three-item version) and CAGE has been mooted (Saunders et al. 1993; Bush et al. 1998). The AUDIT is not specific to older adults and was outperformed by the MAST-G and the CAGE in a study of elderly male veterans (Morton et al. 1996), though more recently the 12-item AUDIT toll has been shown to be effective in the detection of older problem drinkers (Ryou et al. 2012). Buchsbaum et al. (1992) found that the CAGE could discriminate elderly patients with a history of drinking problems. A short version of the CAGE has been used in elderly, i.e., without the first item (C – have you ever tried to cut down), and has been shown to have improved detection on older people (Hinkin et al. 2001).

The SMAST-G (Short Michigan Alcohol Screening Tool – Geriatric Version) (Blow et al. 1992) was developed as the first short form alcoholism screening instrument for older adults. It is a ten-item tool and a score of 2 or more suggests an alcohol problem. It is useful to detect "at-risk" alcohol use as well as alcohol abuse and alcoholism (Naegle 2008). Moore et al. (2002a) also compared CAGE and SMAST-G and found that the SMAST-G identified older adults who were drinking at potentially harmful levels who had not been detected by the CAGE. A combination of both tools was recommended.

The Alcohol-Related Problems Survey (ARPS) and the Short ARPS (shARPS) were created to screen specifically for older adults. Moore et al. (2002a, b) tested these instruments which identify those at risk and found that they were more sensitive than the CAGE, AUDIT, and SMAST-G. Fink et al. (2002) have also demonstrated utility for the short version in elderly outpatients.

A more recent systematic review by Berks and McCormick (2008) has pointed to implementation problems with the ARPS and concludes that the AUDIT is more appropriate for hazardous and harmful drinking while CAGE is better for dependence.

There are fewer tools for the detection of drug misuse. The Drug Abuse Screening Tool is available in several versions with 10, 20, and 28 items, has been used in a variety of different groups, and has been shown to elicit drug abuse and dependence, though not specifically older people (Yudko et al. 2007). Gallagher et al. (2011) have developed a tool for the assessment of inappropriate prescribing which is of huge significance given the prevalence of prescribed medication in older people and the ensuing problems, and it has been suggested that this be used for screening (Lam and Cheung 2012).

Three important additional areas in which it might be prudent to use simple tests are for the assessment of nicotine dependence, cognition, and depression where the Fagerstrom test, the mini-mental state, and the Beck rating scales, respectively, may be handy. In addition to questioning, the "brown bag review" of prescription medication, over-the-counter medication, prescription herbs, vitamins, topical ointments, and dietary supplements may add to the picture of the patient's problems.

Recently Blazer has reported the DAPA-PC, the Drug and Alcohol Problem Assessment for Primary Care. It is a computerized screening system that quickly identifies substance problems in primary care, but it can be used by psychiatrists as well. It is self-administered and Internet based, and since it scores automatically, it generates the patient profile for medical reference and presents unique motivational messages and advice for the patient. It therefore has the advantage of saving clinicians' time, as patients can be screened in the waiting area. It is suggested that this kind of approach may lead to a more honest revelation by patients as compared with face to face assessments where patients may feel ashamed and shy. The point that the elderly will feel more and more comfortable about using technology of this kind is made. This is likely to have important ramifications for enhancing treatment interventions in the future.

128.7 Trials and Guidelines: Targeting Treatment Effectively

There is a need to be positive about where there is evidence and, while there are still uncertainties, embark on good practice (Mayo-Smith 1997; Crome and Bloor 2006; DOH 2007; Lingford-Hughes et al. 2012). There is opportunity to be proactive around factors of resilience that can drive forward improvement, so while taking account of vulnerabilities, not to give it undue and unhelpful focus. The overall theme very often is to conceptualize treatment of older substance misusers as that of the management of chronic disease (NCCMH 2007a, b, 2011; NICE 2007a, b, 2010; NCC-CC 2010). Guidelines are usually dictated by clinical trials. Unfortunately complex patients are excluded: those who are older, those who are substance misusers, and those with comorbidity. Combinations of treatments are rarely studied, and if they are, samples may not be representative of the complex group. There is much ongoing work, yet more to be done, to reverse the persistent exclusion – or discrimination – of older patients from clinical trials.

128.8 Pharmacological Treatments

Lack of evidence of safety in older people is a continuing issue. This chapter will not describe the use of pharmacological agents since this is dealt with in more detail in other chapters in this book. However, there are some relevant issues to consider. Clinical trials of the many agents that have been developed in the last couple of decades have not included older people. Older people may not exhibit withdrawal symptomatology or the severity of withdrawal with which younger people present. Thus, any pharmacological agent should be used with great caution and preferably initiated by specialists in geriatrics and addiction. Monitoring should be frequent, systematic, and regular depending on whether the patient is in hospital, in a nursing home, or in the community. Close scrutiny for adverse effects needs to be undertaken. Some medications may be contraindicated, e.g., bupropion for smoking cessation and nicotine replacement may be preferred. Benzodiazepines should be used sparingly due to accumulation, and this is especially the case for long-acting ones, e.g., lorazepam. It is also important to ensure the enough medication is given, e.g., confusional state due to withdrawal of alcohol, because the risk of fatality is a serious possibility.

Older people should not be denied pharmacological treatment for the management of withdrawal; for the maintenance of abstinence; for the prevention of complications, e.g., Wernicke-Korsakoff syndrome; and for relapse prevention. They should also be adequately assessed and treated for the mental and physical illnesses, since if this does not take place, treatment for the substance use disorder will be undermined and thought to be ineffective. For example, poor treatment for pain relief can exacerbate substance misuse and vice versa. Ineffective treatment for depression can render treatment for substance misuse unproductive. A multidisciplinary team approach is the most appropriate.

128.9 Psychological Treatments

As with the section above, details about the range of psychological treatments available are not detailed to any great extent as this is to be found in other sections of the book. However, the value of the treatments for alcohol, tobacco, and illicit and prescription drugs that have been evaluated in the older population will be described. This draws on a systematic and narrative review carried out in 2007 (Moy et al. 2011). As a result of a literature search, 16 studies were identified. These were carried out between 1984 and 2005, with 14 being published after 1990. Thirteen were undertaken in the USA, two in the UK, and one in Canada. Most (11) were on alcohol, three related to nicotine, one on opiate dependence, and one on prescription medications. The most common settings were five studies in primary care and four in outpatient programs.

The threshold for inclusion was over the age of 50 years, and most studies had a preponderance on male subjects, though one study was only on older women. The ethnicity of the reported studies was mainly Caucasian. Although the mean sample

size was 704 patients, the range was 24–3,622. Eight studies were randomized controlled trials and eight were cohort studies. Patient follow-up was 1 month–5 years and the mean was 18 months. However, less than half of the follow-ups were conducted after one or more years.

Baseline measures for alcohol varied widely, the most popular were the quantity/frequency (5), timeline follow back (4), and Addiction Severity Index (4). Others included the Gerontology Alcohol Project Drinking Profile, binge drinking episodes, weeks abstinent in previous 3 months, age of onset of alcohol use, diagnosis of alcohol abuse/dependence from the Diagnostic Interview Schedule, Composite International Diagnostic Interview – Substance Abuse Module, Quick Diagnostic Interview Schedule, lifetime use, relapse episodes, Drinker Inventory of Consequences, maximum alcohol use, and the Substance Abuse Inventory.

Psychological measures included Gerontology Alcohol Project personal stress inventory, state-trait anxiety, Beck Depression Inventory, Rotter's Locus of Control Scale, Brief Psychiatric Rating Scale, mental health, depressive symptoms, psychological distress, short form (SF-36) questionnaire, symptoms distress checklist short form (SCL-66), mood, and medical outcomes study short form health survey (MOS SF-12).

Outcome measures included mean number of drinks, number of binge episodes, excessive drinking, clinically significant drinking, alcohol consumption measures, Addiction Severity Index, abstinence measures, and quality of life.

Adherence to medication, attendance at therapy, formal aftercare, and informal aftercare were also assessed in some studies.

Interventions were very wide ranging and included the following:

For alcohol: brief interventions (including brief advice, motivational enhancement, or defined by the Medical Research Council or Project TrEAT; based on 12-step, cognitive behavioral; electic; rehabilitation; therapeutic community; general health promotion, ask, advise, assist, arrange; alcohol-specific modules, sessions on many different areas)

For drugs: methadone maintenance

For smoking: medications, e.g., nicotine replacement therapy, bupropion, and different interventions such as advice from GP/nurse, acupuncture, hypnosis, and advice from family and friends

For prescription drug misuse: peer support/education groups, education and counseling, and goal setting

It was acknowledged that the review had limitations which included a reliance on self-report in ten studies, a relatively low cutoff for "older" population, the use of instruments unvalidated in an older population, the representation of treatment-seeking individuals rather than those in need of treatment, treatment that was not designed specifically for older people in general, and the lack of equity in the programs that may downplay positive gains. There was also lack on randomization in half of the studies, selection bias, short follow-up period, small sample sizes, differing treatment populations, programs, settings, and providers, and the majority based in the USA.

However, there are considerable grounds for optimism and both older men and women should be encouraged to seek help for substance dependence (Satre et al. 2003, 2004a, b). Older adults who seek treatment have the capacity to change and do well when compared with younger patients and can be treated outside an age-specific program (Oslin et al. 2002). The number of patients who achieve their follow-up goal is at least as comparable to that of other populations (Dupree et al. 1984); physicians can help older adults who drink excessively (Fleming et al. 1999); patients in elder-specific programs improve across a variety of domains (Blow et al. 2000); older age should not be a barrier to addressing alcohol problems as there is potential for good outcomes and that patients may have achieved better outcomes in elder-specific programs (Lemke and Moos 2003a, b). It is recognized that information about long-term management requires more development (Oslin et al. 2005). These findings were similar to those on smoking, heroin dependence, and prescription drug misuse (Vetter and Ford 1990; Morgan et al. 1996; Brymer and Rusnell 2000; Firoz and Carlson 2004; Schroeder et al. 2006). Intervention by a nurse practitioner led to a decrease in smoking (Vetter and Ford 1990); older smokers benefitted as much as younger smokers (Morgan et al. 1996) and women found interventions helpful, especially light smokers (Schroeder et al. 2006). Firoz and Carlson (2004) dispelled the myth that older people would have worse outcomes than younger people and in fact, nearly twice the number of older people were rated as being "highly successful" compared with younger patients. Brymer and Rusnell (2000) found that patients responded positively to interventions in terms of reduction in substance use, fewer accident and emergency visits, reduced number of hospitalizations, and improved depression scores and activities of daily living. The funding implications were noted in the latter two studies.

The review concluded that older people do not achieve worse outcomes than their younger counterparts: in some cases they may even do better, even though treatments have been developed for younger people. This was considered a positive message which should raise awareness of the issues and the benefits of help. Of course, it is accepted that there are limitations as outlined above. Mainly the diversity of treatment options made it impossible to compare studies which were usually small. More studies on prescription drug misuse and smoking would be important given the projections in prevalence. Standardization of definitions of age and addiction, administration of common tools, description of psychological and pharmacological interventions, utilization of innovative treatment interventions, and delivery in line with best practice for older people would enhance the implementation of improved provision and allow research to evaluate interventions that are more generalizable. There is a reasonably solid basis on which to take such findings forward but most important to underline the fact that age should be no barrier to support.

More recently several studies have been published: Oslin et al. (2006), Lin et al. (2010), Moore et al. (2011), Gallagher et al. (2011), and Zbikowski et al. (2012) on alcohol in primary care, reduction of inappropriate prescribing, and smoking interventions, respectively. Oslin et al. (2006), in the PRISM-E study, compared enhanced specialty referral to integrated care in at-risk patients treated in

primary care. Drinking reduced in both groups at 6 months, and there was no difference between the groups. Thus, a model of care could not be recommended, as the interventions were both active. In another recent study, Lin et al. (2010) reported that 39 % of the older subjects randomized to an intervention comprising personalized risk reports, booklets on alcohol-related risks, and advice from physicians, followed by a health educator call, had reduced drinking within 2 weeks of receiving the initial intervention. Concern about risks, reading educational material, and the perception of physicians providing advice to reduce drinking were associated with early reductions in alcohol use in at-risk individuals. Schonfeld et al. (2010) examined the effectiveness of the Florida Brief Intervention and Treatment for Elders (BRITE) project. This multisite study showed that prescription drug use was the most prevalent substance use problem followed by alcohol, over-the-counter medications, and illicit substances. Those who had a brief intervention improved their alcohol misuse, medication misuse, and depression. Moore et al. (2011) undertook a randomized controlled trial in 631 primary care patients over the age of 55 years. They were given a booklet on healthy behaviors or a personalized report, a booklet on alcohol and ageing, a drink diary, advice, and telephone counseling. At 3 months the intervention group had fewer at-risk drinkers, fewer drinks in the past 7 days, less heavy drinking, and lower risk scores. Both groups demonstrated improvement and at 12 months there was no difference between them. Their conclusion was that a multifaceted intervention does not reduce the proportions of at-risk or heavy drinkers, but it does reduce the amount of drinking at 12 months. Zbikowski et al. (2012) reviewed 13 randomized controlled trials on smoking interventions and concluded that there was a significant intervention effect in 9 studies. Intensive multimodal treatments were more likely to be associated with improved longer-term outcomes, and of particular interest was the study by Hall et al. (2009) that showed the longer-term efficacy of extended CBT without NRT. A compelling trial by Gallagher et al. (2011), the Medication Appropriateness Index (MAI), and the Assessment of Underutilization (AOU) index were used to assess prescribing appropriateness, both at the time of discharge and for 6 months after discharge. Unnecessary polypharmacy, the use of drugs at incorrect doses, and potential drug-drug and drug-disease interactions were significantly lower in the intervention group at discharge. Underutilization of clinically indicated medications was also reduced. Significant improvements in prescribing appropriateness were sustained for 6 months after discharge.

128.10 Safe Limits

A degree of controversy has surrounded the debate about “safe limits” in older people. It should be noted that there is no such thing as a safe limit! Furthermore the recommended limits for adults are very likely not applicable to older people. The US NIAAA has recommended that for some older people one US drink (14 g of alcohol) a day and no more than seven US drinks per week are sufficient. More than three US drinks a day are considered highly likely to lead to harm. Older people

should be advised not to drink and drive, not to use machinery when they have been drinking, and not to swim after consuming drink. It is advisable to eat before drinking and to drink slowly. For those with comorbid conditions, and those on medications, it could be that no drink is the sensible advice (DOH 1995; RCP 1995; Crome et al. 2011).

128.11 Services: Programs and Models

In each country, the constellation of available, or potentially available, services will differ. Commissioners and providers are likely to establish that there are some consistent characteristics that need to be considered to provision. Services need to be "older person friendly." This includes making the referral process easy, ensuring that there are the facilities and information which older people require (DOH 2009; RCPsych 2009). This includes having staff trained in the needs of older people as well as addiction issues including the capability to counter the negativity and negative stereotypes about older people, information which is age specific in content with perhaps simple explanations if required and administered at the pace which is comfortable for older people. In other words, there needs to be a safe, suitable environment which takes account of the person's mobility, sensory, language, and literacy needs.

Older people now comprise the majority of hospital inpatients, so knowledge about the relationship of substance use to common presenting problems needs not only to be rooted in the main psychiatric specialties of old age psychiatry, liaison psychiatry, and addiction psychiatry but also in accident and emergency medicine, geriatrics, general medicine, general practice, and other health professionals, e.g., residential and nursing homes. In the UK, as in most developed countries, there are few models of service provision specifically for this group of patients. The developing world is even more impoverished.

Bartels et al. (2004) undertook a multisite study to determine whether mental health/substance abuse clinics in primary care were more effective than referral to specialist clinics. Seventy-one percent of patients engaged in integrated treatment compared with 49 % in the enhanced referral model. It concluded that older primary care patients were more likely to accept collaborative mental health treatment within primary care than in substance abuse/mental health clinics due to improved access. This has implications for service developments in a group that under use facilities.

The US National Academy of Sciences has produced a report which recommends how the workforce can be prepared to meet the needs of older people with mental health and substance use (IOM 2012). The range of practitioners from those with minimal education to specialists were considered. These included specialists such as general psychiatrists, psychologists, social workers, psychiatric nurses, and counselors; primary care teams including general physicians, general practitioners, nurses, and physician assistants; specialists in the care of older adults such as geriatricians and geriatric nurses, geriatric psychiatrists, gerontological nurses,

geropsychologists, and gerontological social workers; care workers who provide supportive services; peer support providers; and informal care givers, e.g., family, friends, and volunteers. However, their roles were often poorly defined.

It was suggested that as the "baby boom" generation had had higher mental health service use throughout their lives, it was likely that this would continue, although estimates on which to base accurate predictions were not available. However, it was concluded that the requirement for specialist providers was far in excess of that which was available and that this shortage meant that needs would have to be met by a whole range of providers. The report further highlighted the limited opportunities for recruitment to specialization in terms of financial incentives, support, and mentorship. Professional training was not mandatory, so that it was inconsistent, and where progress had been made, programs with promise were not disseminated or evaluated and were therefore at risk of collapse. Strengthening the roles and training of care workers, carers, and families was outlined.

The report further stated:

> A persuasive body of evidence, drawn from two decades of research, shows that two common MH/SU disorders among older adults—depression and at-risk drinking—are most effectively addressed when care is organized to include these essential ingredients: (1) systematic outreach and diagnosis; (2) patient and family education and self-management support; (3) provider accountability for outcomes; and (4) close follow-up and monitoring to prevent relapse. Moreover, these elements are best obtained when care is patient centered (integrating patient preferences, needs, and strengths), in a location easily accessed by patients (e.g., in primary care, senior centers, or patients' homes), and coordinated by trained personnel with access to specialty consultation. There is also evidence suggesting great promise in telehealth and web-based interventions for older adults with MH/SU conditions. Progress in these areas is not likely to be achieved, however, without practice redesign and change in Medicare payment rules. There is a fundamental mismatch between older adults' need for coordinated care and Medicare fee-for service reimbursement that precludes payment of trained care managers and psychiatry consultation. Finally, research on effective delivery of MH/SU care for certain older populations is urgently needed, especially for individuals residing in nursing homes and other residential settings, prisoners, rurally isolated elders, and older adults with severe mental illnesses.

A major hindrance in the implementation of training, treatment, and evaluation is the multiple agencies and departments within government, the voluntary sector, and private organizations that need to collaborate to agree to deliver education, services, and research. Many countries are facing severe reductions in budgets, and this further deters motivation to embark on so daunting a task, about which there is only partial awareness.

128.12 Training and Competencies

Despite recurrent policy recommendations on the need for training, in many countries undergraduate medical students do not have any systematic training in addiction. In the UK a national curriculum has been developed and implemented.

This ensures that every medical student has to be knowledgeable and skilled in tackling fundamental aspects of history taking, diagnosis, and management (ICDP 2007). However, it is recognized that this training needs to be reinforced and updated, so it is being extended to postgraduate medical practitioners so that they can be competent in the management of drug and alcohol problems (RCPsych 2012). A consensus approach between the 13 medical Colleges and Faculties outlines "core competencies which should be incorporated into the curricula for all doctors." It emphasizes three main components: behavior and attitudes, knowledge, and skills. Importantly, it stresses the need for feeling comfortable and confident when discussing addiction issues with patients, working in a supportive, nonjudgmental, and non-confrontational manner, and taking appropriate action with regard to their own or colleagues' misuse of substances. It describes the areas in which practitioners should be knowledgeable, e.g., the addictive potential of alcohol and drugs including prescribed and over-the-counter medications; the acute effects of intoxication, the chronic harms, and common presentations of problems related to substance use; the range of interventions available; recommended "safe" limits for alcohol; and the impact on the family and community as well as on the individual. Doctors across all specialties need to be competent in the screening, assessment, diagnosis, provision of brief interventions, and further management or referral of substance misuse patients. It notes that while 1.6 million people are alcohol dependent in the UK, only 6 % receive the treatment they need. While this is not specific to older people, the general principle is pertinent, given that the majority of patients are in the older age group. Specialist provision is dwarfed by the prevalence. Expansion in interprofessional training, mentorship, making the experience of working in this area a positive one, and financial arrangements to support training and service development is recommended (IOM 2012).

128.13 Future Prospects: A Matter of Principle

Some fundamental recommendations which can be implemented immediately encompass inclusion of older substance misusers in all relevant policy documents and in all clinical trials related to substance problems. Furthermore, older people with substance problems should be a focus of training in all medical and allied professionals throughout their professional career and should be a priority area for research. Research into the nature and extent, the predictors and preventive potential, and the adaptations of successful treatment and novel interventions is of high priority, though there is sufficient information to insist that, without delay, detection, intervention, and development of care models that are likely to improve the health and well-being of older people are instituted.

This is an area that should be of concern to all clinicians: old age psychiatrists, addiction specialists, geriatricians, nurses, psychologists, social workers, and their teams. It should be of interest to researchers in gerontology, sociology, and economics and to policy makers and commissioners. How we decide on

provision for this group of people is a measure of how we treat some of the most vulnerable and disenfranchised people in our communities.

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Addiction and Lesbian, Gay, Bisexual and Transgender (LGBT) Issues

129

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Contents

Abstract

This chapter examines addiction issues particular to lesbian, gay, bisexual, and transgender (LGBT) people. This includes a description of the available epidemiological data on substance use and addiction in the LGBT community, as well as a discussion about unique psychosocial issues that LGBT people face that increase their risk of substance use, such as stigma, social rejection, discrimination, harassment, HIV, issues specific to adolescents and young adults, internalized homophobia, and transphobia. Because the vast majority of research on substance abuse in the LGBT community is from North America, examples of social settings and substances specific to this LGBT community are used to illustrate how specific drugs can develop a unique appeal to an LGBT community in response to the psychosocial environment and stressors that a specific LGBT community faces. Substances discussed include methylenedioxymethamphetamine (MDMA, ecstasy), methamphetamine, gamma-hydroxybutyrate (GHB), anabolic steroids, and cross-gender hormones. In other LGBT communities, different psychosocial

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stressors lead to unique substance abuse patterns that must be understood to adequately treat addiction in those populations. General recommendations are made regarding the provision of clinically competent care for cases of LGBT addiction, and common clinical scenarios are discussed. The need for research on substance abuse patterns in LGBT populations is sternly emphasized in order to improve understanding of local patterns of substance abuse and to improve the provision of treatment to those populations.

129.1 Introduction

Addiction among lesbian, gay, bisexual, and transgender (LGBT) people requires special attention because patterns of substance use and abuse differ markedly between LGBT people and the general population. Studies examining LGBT addiction, which will be detailed below, indicate a higher prevalence of substance use disorders among LGBT people. Despite the increased risk of addiction, there is a relative lack of research studying the prevalence, causes, and consequences of LGBT addiction. In addition, training clinical training programs incorporate little to no education specific to LGBT people (Makadon 2006; Tesar 1998).

LGBT people face unique psychosocial stressors that lead to an increase in addictive substance use. Many of these people use drugs and alcohol as a way of coping with these stressors, which are largely related to homophobia and transphobia (transgender phobia). Examples include adolescents who are rejected by parents and become homeless, sometimes resorting to sex work in order to survive; people who lose their jobs or housing because of homophobia and have no legal recourse; people who are verbally harassed or physically assaulted because of their sexual orientation or gender identity; and people who hear repeated denigration of homosexuality in their religious places of worship. All of these examples can cause an immediate negative psychological response, but over time such events may also be insidiously incorporated into an individual's sense of self, resulting in the self-hatred of internalized homophobia.

LGBT people also have particular consequences of substance abuse. For example, methamphetamine use in North America has a much higher prevalence among gay men compared to the general population, and in this community it has a strong association with unprotected anal intercourse. As a result, gay men in North America have a significantly higher risk of infection with HIV or other sexually transmitted diseases (Lee 2006).

Clinicians must be familiar with LGBT-specific issues so that they can adequately understand and treat addiction in this population. However, because of the lack of clinical training in LGBT issues, most addiction specialists are not prepared to effectively treat LGBT addiction. In response to this need for improved LGBT treatment, LGBT-specific treatment programs have been developed. The goal of this chapter is to familiarize the general addiction clinician with the most relevant LGBT issues to improve the availability of competent clinical services to this population.

Unfortunately, the vast majority of date pertaining to drug use and addiction among the LGBT people is limited to North America. Because of the wide variation in cultures and local conditions in which people live, this chapter is not able to describe the issues and make specific treatment recommendations for the people of all countries. Rather, this chapter provides examples of challenges that some LGBT people face and how they may resort to substance use as an attempt to cope. At the conclusion of this chapter, consideration will be given to how the information in this chapter may be useful to clinicians from countries outside of North America.

129.2 LGBT Features

129.2.1 Epidemiology

Data on the prevalence of substance use and substance use disorders among LGBT people in North America vary widely, though most studies show higher rates when compared to either the general population or heterosexuals. Early studies had significant methodological problems, such as inconsistent definition of homosexuality, nonstandardized measures of substance use, small homogenous samples, lack of controls or comparison groups, and considerable sampling bias. For example, some studies obtained their study samples from gay bars – at one time the only place where gay men could be found because most hid their sexual orientation – which likely inflated the observed rate of alcoholism (Anderson 2009). Most studies and reports estimated an incidence of approximately 30 % among LGBT people, compared to 10–10 % for the general population (Cabaj 1996).

More recent research does not show such high prevalence, but continues to find an increased rate of drug and alcohol use and dependence among LGBT people (Cochran et al. 2003; Drabble et al. 2005; Fergusson et al. 2005; Hughes and Eliason 2002; McCabe et al. 2009; Meyer et al. 2003; Wilsnack et al. 2008). Cochran et al. (2004) found a moderate elevation of drug, particularly marijuana, use dependence in gay and bisexual men and women when compared to heterosexuals.

A more recent study by McCabe et al. (2009) examined US data with a large national sample of 34,653 from the 2004–2005 (Wave 2) National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), finding that 16.8 % of gay-identified men met DSM-IV criteria for past-year alcohol dependence compared to 6.1 % of heterosexual-identified men, 0.6 % of gay-identified men met criteria for marijuana dependence compared to heterosexual-identified men, and 3.2 % of gay-identified men met criteria for other drug dependence compared to 0.5 % of heterosexual-identified men. Among females, 13.3 % of lesbian-identified women met criteria for past-year alcohol dependence compared to 2.5 % of heterosexual-identified women, 2.8 % of lesbian-identified women met criteria for past-year marijuana dependence compared to 0.2 % of heterosexual-identified women, and 5.7 % of lesbian-identified women met criteria for past-year other drug dependence compared to 0.4 % of heterosexual-identified women.

Other studies showed little difference between the patterns of alcohol use among gay and bisexual men compared to heterosexual men. However, other drug use was found to be higher among urban gay and bisexual men (Drabble et al. 2005; Stall et al. 2001). Several studies, however, found that lesbians had higher rates of heavy alcohol consumption and alcohol dependence, as well as more alcohol-related problems and a higher likelihood of prior substance abuse treatment compared to heterosexual women (Gruskin and Gordon 2006; Roberts et al. 2005; Drabble and Trocki 2005).

Overall, recent research has found that nonheterosexual orientation is associated with a higher risk of substance use and dependence. This higher risk should inform more targeted efforts in the development of intervention and primary prevention.

129.2.2 Psychosocial Issues Unique to LGBT Individuals

While rates of substance use disorders vary widely among studies, research data is consistent in showing that prevalence of substance use in the LGBT community is higher than the general population. Early on when homosexuality was considered a mental disorder, it was hypothesized that homosexuality itself was the cause of increased rates of alcoholism (Israelstam and Lambert 1983). However, this notion has never been proven and has long been discarded (Israelstam and Lambert 1986). Instead, research has found that LGBT people face unique stressors because of their minority status, such as harassment, discrimination, violence, and social rejection. All of these stressors are associated with higher rates of substance abuse, regardless of sexual orientation or gender identity. The following section will describe the particular stressors that LGBT face and how they relate to substance use as a maladaptive way of coping.

129.2.2.1 Stigma and Phobia Based on Sexual Orientation and Gender Identity

The most common problems that LGBT people face all stem from homophobia, heterosexism, and transphobia. A review of 24 separate studies looking at anti-gay experiences found that 80 % of respondents had been verbally harassed, 44 % of respondents had been threatened with violence because of their sexual orientation, 33 % had been followed or chased, 25 % had objects thrown at them, and 13 % had been spit upon (Berrill 1992). When individuals become the victims of such attacks, their sexual orientation itself becomes a source of pain and danger. As victims try to make sense of their attacks, many internalize the beliefs of their aggressors, and they believe that the attacks were justified punishments for being gay. This internalized self-hatred can lead to profound feelings of anxiety, helplessness, and depression (Garnets et al. 1990). Alcohol and drugs are common ways to attempt to deal with anxiety and depression. This is not a reaction specific to the LGBT population. Studies sampling the general population find that victimization, violence, trauma, and ostracism have all been associated with increased rates of substance use (Alegria et al. 2010; Johnson et al. 2010; Khoury et al. 2010).

Heterosexism pervades American society, and legally sanctioned discrimination is still common. At the time of this writing, anti-sodomy laws persist in over half the state of the United States, same-sex marriage is not legal in 44 states, and in most places there are no legal protections against discrimination based on sexual orientation. Under President Barak Obama, the ban on gays in the military was finally lifted, with heavy opposition by right-wing conservatives. In a telephone survey conducted by the San Francisco Examiner, 47 % of gays and lesbians reported some form of discrimination with jobs, housing, health care, or in other settings (San Francisco Examiner 1989).

Repeated discrimination causes a profound sense of victimization, and the lack of legal policies to protect LGBT people from discrimination leaves LGBT people feeling even more helpless. With no institutionalized protections, the message to LGBT people is that society as a whole rejects them. In contrast, heterosexuals who experience discrimination based on race, religion, or some other nonsexual orientation issues have legal protection and can take recourse. This deepens the sense of helplessness of LGBT people, and alcohol and drugs become a common way to cope with this ongoing pervasive stress. A study by the University of Michigan found that over two thirds of gay, lesbian, and bisexual adults surveyed had experienced discrimination based on sexual orientation, race, or gender. Those who reported all three types of discrimination were four times more likely to have a current substance use disorder compared to those who did not report discrimination (McCabe et al. 2010).

Through the process of "coming out" or making one's sexual orientation explicitly known to others, as well as fully acknowledging it to oneself, many LGBT people are able to overcome the negative impacts of heterosexism, homophobia, and transphobia. However, LGBT people who have not come out, continue to wish that they were heterosexual or to deny their true gender identity, or have little contact with the LGBT community are found to experience greater psychological distress (Bell and Weinberg 1978; Hammersmith and Weinberg 1973; Maylon 1982; Weinberg and Williams 1974).

Some people who still feel intense self-hatred may use mood-altering substances to numb or lessen feelings of fear, anxiety, or self-loathing. Certain substances disinhibit people, allowing them to act out the natural sexual urges that their internalized homophobia condemns. In both these situations, relief is only temporary, and during withdrawal from drugs or alcohol, the negative feelings can be intensified, increasing the likelihood that a person will use those substances again to experience relief.

129.2.2.2 HIV and AIDS

HIV continues to be a significant problem faced by the LGBT community. Dealing with HIV involves coping with multiple medical issues, as well as the stigma associated with HIV and AIDS. For most, the process is a difficult one, and psychiatric symptoms such as depression, anxiety, fatigue, sleep disturbances, and memory problems are common. One study of HIV-infected people in North Carolina found that 60 % of study subjects reported psychiatric symptoms

(Whetten et al. 2005). Another study found that 54 % of people living with HIV reported symptoms of depression in the past week (Eller et al. 2010).

The emotional stress caused by HIV puts HIV-positive people at increased risk of developing problems with substance abuse, as they may use substances to manage difficult emotional states. Sedating drugs such as alcohol, sedatives, and opiates decrease anxiety and emotional pain or assist with psychological attempts to deny one's problems. Stimulants such as cocaine and methamphetamine elevate depressed mood, distract one's attention from current problems, and combat certain symptoms of HIV infection, such as fatigue and decreased libido (Nakamura et al. 2009; Prestage et al. 2009). Methamphetamine in particular has become popular among some MSM with HIV. Some report that methamphetamine helps them overcome feelings of isolation through a sense of connectedness to other HIV-positive MSM who also use methamphetamine, making up an underground community of antiestablishment methamphetamine users. This rebellious counter-culture attitude of methamphetamine use gives some HIV-positive men a sense of empowerment that lessens feelings of helplessness. Indeed, substance use rates are elevated among people with HIV. In one study of HIV-positive MSM, 64 % reported alcohol use, 36 % reported marijuana, 27 % used nitrate inhalants ("poppers"), 13 % used cocaine, and 12 % used amphetamines/methamphetamine (Purcell et al. 2001).

In addition to the addictive and mood problems associated with substance use, several substances have been found to accelerate the disease progression of HIV. Frequent consumption of alcohol is associated with both increased viral load of HIV and decreased number of CD4 lymphocytes. The decline in immune function is the result of both decreased adherence to HIV medications and a direct effect of alcohol on immune cells (Baum et al. 2010). Stimulants such as cocaine, amphetamines, and methamphetamine accelerate the spread of HIV in certain immune cells that introduce HIV into the brain (Gaskill et al. 2009). Methamphetamine in particular has been shown in numerous studies to increase replication of HIV and accelerate brain damage caused by the virus (Nair et al. 2010; Marcondes et al. 2010).

Another concern about drugs of abuse and HIV is the increased risk to HIV-negative people of contracting HIV. All mood and consciousness-altering substances can affect sexual behavior and decisions about taking precautions to protect oneself from HIV infection. Several studies have demonstrated increased casual sex and decreased condom use associated with the use of alcohol, marijuana, and methamphetamine (Hasse et al. 2010; Hendershot et al. 2010; Townsend et al. 2010).

129.2.2.3 Ethnic Minority Status

Individuals who are "double minorities" – sexual minorities and ethnic minorities – face many challenges that are often not understood by others. In addition to the discrimination and stigma that each group deals with, there is additional stress from the conflict that arises between the two minority identities. Certain ethnic groups have particularly strong homophobic beliefs, with inflexible

ideas about gender behavior. The mainstream, predominantly Caucasian LGBT community, may be so culturally different from one's ethnic community that one often feels caught between the two worlds. Choosing one community over another can leave people with a guilty feeling that they have abandoned the other community, and those individuals are forced to deny a part of their identities. This intense psychological stress increases the likelihood that ethnic minority LGBT people will use drugs or alcohol. In one study of black gay men who use methamphetamine, the drug was identified by users as a coping tool for depression and anxiety; stigmatization from sexual identity, race, and or HIV status; and feelings of being excluded from both the black community and the white gay community (Halkitis 2009; Halkitis and Jerome 2008; Jerome 2007).

Various studies have found increased rates of drug and alcohol use among black and Hispanic men who have sex with men. A New York-based study found that African-American MSM reported a significantly higher number of drinks per occasion compared to other ethnicities (Irwin and Morgenstern 2005). In a study of gay men recruited from gyms, African-American men were almost twice as likely to report use of methamphetamine compared to white men (Halkitis et al. 2008). Studies of Hispanic gay men have similar findings. Methamphetamine use has been found to be higher in those Hispanic gay men who choose the mainstream gay community over their Hispanic communities and who have less language attachment to those communities (Fernandez 2005, 2007). A study of transgendered people of color in Washington, DC, found that 48 % of those surveyed reported a substance abuse problem (Xavier et al. 2005). There is an unfortunate lack of research examining the prevalence of substance abuse among ethnic minority lesbians.

Ethnic minority LGBT community organizations are important resources that address the difficulties that double minority individuals face. They offer experienced support, as well as reinforce the belief that one does not have to choose between one's ethnicity and sexual orientation or gender identity.

129.2.2.4 Youth and Coming Out

Adolescence is a developmental stage that is associated with experimentation and substance use. In addition to the usual difficulties of adolescence, LGBT youth have the additional challenge of trying to understand their sexual orientation and gender identities and dealing with stigma from largely heterosexist peers. Trying to cope with homophobic attacks, both physical and psychological, and risking rejection by peers, family, and teachers, LGBT teens often feel helpless and alone. This increased psychological stress during a time when teens are already experimenting with alcohol and drugs puts LGBT adolescents at significant risk of developing substance abuse problems. Alcohol and drug use early in life significantly influences substance use patterns later in life, and substance abuse among LGBT teens can lead to serious addictive problems in their adult years (Parks et al. 2007).

A study of students in Illinois found that the youth who identified as gay, lesbian, or bisexual and the youth who were questioning their sexual orientation were more likely to report high levels of bullying and victimization compared to the

heterosexual youth. Those who were questioning were found to have the highest levels of bullying compared to the heterosexual youth, as well as those with firmly established LGBT identities. High levels of bullying were found to correlate with higher levels of depression, suicidal thoughts, and substance use (Birkett et al. 2009).

Family acceptance is extremely important to the psychological well-being of adolescents. Unfortunately coming out threatens family acceptance for many LGBT youth. A San Francisco study looking at the effects of family rejection of sexual orientation and gender expression showed that gay, lesbian, and bisexual young adults who reported high levels of rejection during adolescence were 8.4 times more likely to have attempted suicide, 5.9 times more likely to report high levels of depression, and 3.4 times more likely to use illegal drugs, compared with gay, lesbian, and bisexual young adults who reported little or no rejection from their families (Ryan et al. 2009).

Homelessness is a tragic consequence for many LGBT youth who are rejected by their families. Homeless youth who are sexual and ethnic minorities are at increased risk of resorting to sex trade for survival (Walls and Bell 2010). In addition to physical danger, the sex trade exposes youth to drug use. Drugs are often used to enhance the psychological state required to do sex work, and drugs and alcohol are also used to cope with the stresses of resorting to sex work.

The behavior of role models significantly shapes attitudes that young LGBT people have about alcohol and drugs. For those newly coming out, bars and clubs are the first significant social contact that many youth have with the LGBT community. Drinking and club-drug use become normalized early, and for some individuals, drugs and alcohol become an integral part of their social and sexual behavior. This topic will be discussed further in the section on social venues as triggers for substance abuse.

LGBT adolescents encounter numerous life stresses that are associated with increased drug and alcohol use, and indeed, many research studies have found elevated rates of substance use among these teens (Birkett et al. 2009; Coker 2010; Ryan et al. 2009). Gay, lesbian, and bisexual youth report higher initial rates of substance use, and their use over time increases more rapidly than heterosexual youth (Marshal et al. 2009). One study found that gay, lesbian, and bisexual youth are 190 % more likely than heterosexual youth to use alcohol or drugs. In particular, bisexual youth are 340 % more likely, and females are 400 % more likely to use drugs or alcohol compared to heterosexual youth (Marshal et al. 2008).

Research indicates that there are concrete ways of addressing some of the causes of such high rates of substance use in LGBT youth. Schools have the ability to affect health outcomes and decrease drug and alcohol use in LGBT teens by creating positive climates for sexual minority youth and instituting policies that actively address bullying and homophobic teasing. In addition, schools, community programs, or other social services can decrease LGBT substance abuse by working with LGBT youth and their families to provide education and foster greater family acceptance.

129.2.2.5 Social Settings as Triggers for Substance Use

Historically, one of the earliest settings where LGBT people could meet socially was bars. Similar to the days of prohibition, gay bars were discreet underground places where LGBT people came secretly to find other LGBT people, whether for sexual encounters or for simple social connection. After the Stonewall riots, which broke out after the police raided a gay bar in New York City's Greenwich Village, gay bars became a community institution, no longer just providing a place to congregate, but also becoming a symbol of the gay community's right to exist.

Because of the importance that bars hold in the LGBT community and the lack of other social institutions that fulfill the community's needs, bars have become the focus of social life for many LGBT people. To frequent a gay, lesbian, or transgender bar was to be socially connected and to feel part of a community, when LGBT people otherwise felt isolated. For many people, drinking became associated with positive feelings of group membership. In addition, alcohol helped decrease the anxiety of coming to a secret place, hidden from heterosexual people. It helped with the anxiety of meeting new friends or sexual partners, and it helped to medicate difficult feelings around one's sexual orientation and gender identity. For many people, alcohol is present during their first social experiences in the LGBT community and first same-sex sexual encounters, and for some it becomes an integral part of these experiences in the future. A strong association is established between alcohol and most aspects of socializing, and the increased exposure to alcohol increases the risk of developing alcohol use disorders.

Circuit parties are a popular venue with some gay men that exposes them to extremely high levels of drug use. Circuit parties began as private house parties in the 1980s that grew in size to large-scale parties with thousands and sometimes over 10,000 people. These parties are sexually charged, with men dancing shirtless and with very little clothing. Sexually uninhibited behavior often occurs on the dance floor or in back rooms. For many gay men, who may travel thousands of miles to these events, circuit parties are a celebration of sexual liberation. In contrast to the social rules of a generally heterosexist society, circuit parties encourage openly gay sexual expression, and for many gay men, they are an important social ritual that helps to define their gay identity.

Club drugs [methylenedioxymethamphetamine ("ecstasy"), ketamine ("Special K"), gamma-hydroxybutyrate ("GHB"), and crystal methamphetamine] are commonplace at circuit parties. Many of these drugs enhance the experience of liberation, social bonding, and sexual disinhibition that partiers seek. In fact, drug use is the cultural norm at these events (Mattison et al. 2001; Lee et al. 2003; Ross et al. 2003; Weidel et al. 2008). A San Francisco survey of gay men who attended circuit parties found that 80 % of survey respondents used ecstasy, 66 % used ketamine, 43 % used crystal methamphetamine, 29 % used GHB, 14 % used sildenafil (Viagra), and 12 % used amyl nitrite ("poppers"). More than half of survey respondents in one study used four or more drugs at the same event (Colfax et al. 2001).

Club-drug use is an integral part of circuit parties, and for some gay men, circuit parties are their first exposure to these substances. While the initial motivation for attending circuit parties is usually social, drugs become so intertwined with the experience that they gradually become one of the predominant reasons people attend. A survey of 1,169 gay men who attended circuit parties found that while the majority of party goers were attracted to the social aspect of the parties, 13 % identified three or more of their motivations to be related to drugs and sex (Ross et al. 2003).

While the Internet is not a physical space, it is a virtual setting in which increasing numbers of LGBT people connect and communicate. People who live in remote areas or in communities with few LGBT members are able to contact and exchange ideas with others, and this new social setting decreases the sense of isolation felt by many people who otherwise would have little contact with other LGBT people. For those in urban or suburban areas, the Internet has become the new gay bar, serving as the place where many people go searching for companionship or sex. Gay men, lesbians, and bisexuals are more likely than heterosexuals to use Internet personal ads to meet others (Lever et al. 2008), and surveys estimate that 33–51 % of gay men have used the Internet to meet other men (Ogilvie et al. 2008; Bolding et al. 2005; Chiasson et al. 2007).

Although bypassing the bar and club scene seems like it would reduce alcohol and drug consumption, the Internet has become an active meeting place for gay men seeking methamphetamine-fueled sex. A culture and language has developed around Internet methamphetamine sex, with commonly used terms such as "PNP" (short for "party and play") and "chemistry-fueled sex," both referring to sex with methamphetamine. Many men report that they were first exposed to methamphetamine through sexual partners they met on the Internet.

One of the effects of methamphetamine is a dramatic increase in sexual desire and pleasure. During methamphetamine binges, some men have sex for hours to days, sometimes with multiple partners, with little to no sleep. The intense focus on sexual pleasure is so strong that some men decide against using condoms during anal sex (Mansergh et al. 2006; Mimiaga et al. 2010; Balan et al. 2009; Taylor et al. 2007), and methamphetamine is likely one of the major reasons for the increasing rate of new HIV infections among gay men each year. The Internet serves as a way of connecting methamphetamine users and providing them with easy access to drugs and sex. In fact, there has been a growth of underground member-only websites where members share videos of sex and injecting methamphetamine, and members openly discuss seeking drug-fueled sex. This ability of methamphetamine users to remain hidden from others through the use of the Internet has made it difficult for education and outreach services to reach them. Consequently, they do not access treatment services until much later, when their addiction is more severe. Recent research has been investigating online interventions to help MSM decrease their HIV-risk behavior (Rhodes et al. 2010; Chiasson et al. 2009). Similar online interventions need to be developed to reach the online community of gay male methamphetamine users.

129.2.3 Treatment and Obtaining Culturally Competent Care

129.2.3.1 LGBT-Specific Treatment Programs

The first addiction treatment center to offer services specifically for LGBT people was the Pride Institute in Minnesota, which opened its doors in 1986 (Ratner 1988). Since that time, a small number of programs have emerged that cater exclusively to LGBT clients. These programs usually have several LGBT clinicians and staff, and those who are not LGBT are screened for their sensitivity to LGBT people and issues. They are supportive environments where sexual orientation and gender identity are not stigmatized, and homophobia and transphobia do not pose treatment barriers to clients. If a person encounters homophobia or transphobia in the treatment setting, feelings of victimization and isolation make it difficult to experience the support from fellow clients and staff that are necessary for therapeutic change. LGBT programs have specialized knowledge about clinical issues common to LGBT substance abuse clients, such as stigmatization, victimization, coming out, histories of rejection by family of origin or peers, internalized homophobia, sexual addiction, same-sex domestic violence, and HIV. These clinical issues are often related to the development of substance abuse and addiction, and in these specialized programs, they can be explored in depth by experienced clinicians in a nonjudgmental environment.

After the Pride Institute opened in 1986, a handful of other private organizations opened to serve the LGBT community. Alternatives, located in Los Angeles, CA, offer inpatient rehabilitation, as well as intensive outpatient treatment. Smaller organizations, such as New Leaf Services in San Francisco and Montrose Counseling Center in Houston, TX, provide solely intensive outpatient services, with individual counseling and group therapy.

Some LGBT-focused health centers in metropolitan areas have expanded their programs to include chemical dependency treatment services. Examples include the Fenway Community Health Center in Boston, the Howard Brown Health Center in Chicago, the Whitman-Walker Clinic in Washington, DC, and Lyon-Martin Health Services in San Francisco, a facility specializing in the care of lesbian, bisexual, and transgendered women.

The demand for LGBT-focused addiction treatment centers remains high, and some LGBT community centers have developed addiction services to address their local community needs. An example is Center Care Recovery at the LGBT Community Center of New York, which has become a fully state-accredited addiction treatment program. The Los Angeles Gay and Lesbian Center offers outpatient individual and group counseling, with a particular focus on crystal methamphetamine.

Another way that LGBT services have grown is through the development of LGBT "tracks" or dedicated units within a general population treatment facility. An example is the LGBT Inpatient Treatment Program at Brattleboro Retreat, a historic facility dating back to 1834, with a pioneering philosophy of humane treatment of mentally ill patients. Smaller organizations have incorporated LGBT tracks into their programs, such as the Realization Center, an outpatient addiction treatment

facility in New York that offers clients in their general program the option of gay-focused support groups. Unfortunately, while many organizations may market themselves to the LGBT community, it is questionable whether they actually provide LGBT-specific services. In a 2004 study looking at substance abuse treatment programs in the United States and Puerto Rico, 11.8 % of the programs claimed to offer LGBT-specific services. However, of that 11.8 %, 70.8 % were no different from substance abuse treatment programs for the general population (Cochran et al. 2007).

Because of the small number of LGBT programs and the limited options available, many people wonder how essential LGBT-specific services are to recovery from chemical dependence. LGBT-focused programs are helpful options for people who are struggling with coming out and are not yet comfortable discussing their personal lives; people for whom inner conflict about one's sexual orientation or gender identity is a significant factor in their drug or alcohol use; trauma victims of homophobic or transphobic attacks; and people for whom drug-associated activities, such as compulsive sex with methamphetamine, are difficult to discuss in a general population setting. Otherwise, if a general treatment program is welcoming and supportive, it can be equally effective at helping someone achieve sobriety. A study of 162 - methamphetamine-using gay men looked at the outcome of those randomized to general treatment versus gay-specific treatment. While those who were in the gay-specific treatment showed a greater reduction in risky sexual practices, such as anal sex without using condoms, there was no difference in the rate of abstinence between the gay-specific and the nonspecific treatments (Shoptaw et al. 2005). While there are some clear benefits to LGBT-specific programs, such as greater comfort in discussing important life stresses, it is important to understand that significant benefit can be achieved at any program that is generally supportive.

129.2.3.2 Finding Clinically Competent Care

Clinical training in LGBT issues is generally lacking in all the mental health-related fields, including social work, psychology, and medicine (Hellman 1996; Makadon 2006; Tesar and Rovi 1998). A survey of 116 medical schools with departments of family medicine found that over half of the schools did not address homosexuality or bisexuality at all. For those that did, an average of 2.5 h total over the course of a 4-year program was devoted to addressing LGBT issues, mostly in the format of lectures on ethics and human sexuality (Tesar and Rovi 1998). The field of social work has been more active in advancing LGBT education. In 1991 the Council on Social Work Education established a requirement that content on sexual orientation be included in all accredited social work programs.

Educational requirements for certified drug counselors vary by state. In New York State, the Office of Alcoholism and Substance Abuse Services (OASAS) recognizes the importance of understanding specific community issues in working with substance abuse clients, and OASAS strongly recommends the inclusion of

racial and ethnic special needs to be in training curricula, yet there is no such recommendation for LGBT issues in education. This author is not aware of any state that requires LGBT content in drug counselor training programs.

A study of urban and rural drug counselors' attitudes about LGBT clients found that both groups had little formal education about LGBT issues, and more than half of counselors had negative or ambivalent attitudes toward LGBT clients. Many of the counselors lacked knowledge of basic social issues that impact LGBT drug and alcohol use, such as internalized homophobia, issues relating to family of origin and current family, and relevant legal issues. Although urban counselors had more contact with LGBT clients and underwent more LGBT-specific education than rural counselors, they did not report any more positive attitudes or knowledge of relevant LGBT issues compared to the rural counterparts (Eliason and Hughes 2004). More extensive education about LGBT issues and training around LGBT sensitivity is needed for clinicians at all levels to more effectively treat LGBT substance abuse clients.

129.2.3.3 Should My Care Provider Be LGBT?

There is significant debate as to whether LGBT clinicians are better suited to work with LGBT substance abuse clients. Heterosexual counselors and those with few LGBT friends have been found to have stronger negative biases against LGBT individuals compared to LGBT counselors (Cochran et al. 2007). A study of 126 gay, lesbian, and bisexual-identified people divided subjects into two groups: one group was read a vignette of a counselor that used heterosexist language; the second group heard the same vignette with the heterosexist language removed. Significantly more respondents responded positively to the vignette free of heterosexist language, and those respondents were much more likely to return to see the counselor, to disclose their sexual orientation, and to discuss personal information (Dorland and Fischer 2001). There is plentiful research examining the effect of similarities between therapist and client. One study looking at African-Americans found that those engaged in treatment with African-American therapists felt better understood and accepted, and they described a better rapport with their therapists, as well as an ability to be open in sessions (Jones 1978). There are similar findings for matching other ethnicities and gender. In addition to client comfort level, the LGBT therapist may have greater familiarity with client's experiences, such as growing up as a minority in a heterosexist society or experiencing unresolved internalized homophobia. The client can spend less time in therapy explaining these phenomena to an inexperienced therapist, and therapeutic work can begin more quickly. An LGBT therapist who is open about his or her sexual orientation or gender identity can also serve as a role model for the client.

Together with the advantages of LGBT therapists, there are many potential pitfalls. The most common difficulty is the therapist overidentifying with the client. Both therapist and client may assume that because they share some experiences, their reactions to those experiences are the same. The therapist may make incorrect assumptions about the client or may fail to explore a topic that was insignificant in

the therapist's personal experience but was traumatic to the client. Therapists may have difficulty keeping an open mind to reactions different from their own and may incorrectly perceive their own views in the clients, rather than being able to understand the clients as they really are. Lastly, a client who feels doubts and fears about being LGBT may be reluctant to fully disclose his or her negative beliefs to a therapist who is openly LGBT, and those fears may be more difficult to explore and resolve.

LGBT clinicians are not necessarily less inclined to heterosexist beliefs than heterosexual clinicians. Growing up in a heterosexist society, all people absorb some degree of heterosexist beliefs, even if only subtly or outside of conscious awareness. Researchers have described some lesbian, gay, and bisexual therapists as more homophobic than heterosexual therapists (McHenry and Johnson 1993), and because the homophobia may be less apparent or unexpected in those therapists, the therapist could have a greater impact in undermining the client's self-esteem and reinforcing negative beliefs about the self. While it remains unclear if the clinician's sexual orientation per se is important, heterosexual bias in any clinician makes a clear difference in clients' experiences.

There are many ways in which heterosexism can affect a client's treatment. For example, a clinician who believes that homosexuality is fundamentally wrong may assume that all of a client's problems stem from his or her sexual orientation, overlooking the other life issues that may be hurting the client's emotional life. The therapist might also fail to appreciate the degree to which societal heterosexism adversely affects the client and causes drug or alcohol use because the therapist believes that the heterosexism is justified and that the client must work to accept it. Clinicians who believe that homosexuality is shameful may encourage a client to remain secretive about his or her sexual orientation and may fail to help the client through the important life stage of coming out and developing a stronger and more positive self-image. This collusion with a client's internalized homophobia could worsen the internal conflict of a client who hates himself or herself, and this could result in worsening of alcohol and drug use.

Bisexual clients can experience unique difficulties from both heterosexual and gay or lesbian clinicians. Common assumptions about bisexuals are that they are unable to commit to relationships, they are unfulfilled unless they are simultaneously in relationships with both sexes, and they are in denial about being gay or lesbian (Dworkin 2001). Bisexuals suffer misunderstanding and discrimination from both heterosexuals and gay and lesbian people, and in some ways they can feel even more isolated and invalidated. An Australian study of 4,824 adults found that bisexuals scored highest on measures of anxiety and depression, compared to gay men, lesbians, and heterosexuals. Bisexuals reported more current adverse life events, greater childhood adversity, less positive support from family, and more negative support from friends (Jorm et al. 2002). Clinical assessments made with prejudices and incorrect assumptions may be inaccurate, and the actual life problems that underlie a bisexual person's substance use may not be recognized and properly addressed.

Transgender clients are perhaps the worst victims of phobic reactions by clinicians. Substance abuse counselors express even more negativity and feel they know even less about transgendered people than gay men, lesbians, and bisexuals (Eliason 2000). Some examples of transphobia include assuming that a transgendered person is mentally ill on the basis of his or her gender variance, recommending therapy to change a transgendered person's gender identity against that person's stated needs and goals, and withholding approval for gender reassignment treatments and procedures, such as hormones and surgery (Raj 2002). Transgendered people are also victims of physical and verbal abuse by staff in residential treatment settings, are often forced to wear clothes not consistent with their gender identity, and are forced to bathe and sleep in areas not of their gender identity (Transgender Substance Abuse Treatment Policy Group of the San Francisco Lesbian, Gay, Bisexual, and Transgender Substance Abuse Task Force 1995). For this group, transphobic treatment providers become an active part of the root cause of their substance abuse. It can be difficult, if not impossible, for a transgendered person to benefit from a clinician or treatment program unless transphobia is effectively addressed.

It is important to emphasize that any therapist, regardless of sexual orientation or gender identity, can have negative attitudes or reactions to LGBT clients. For example, a feminist lesbian doctor may react with feelings of anger or loathing at a male-to-female transgendered patient who has had breast augmentation surgery and dresses in highly seductive female clothing, feeling that the patient is perpetuating the sexist feminine ideals of a male-dominated culture. A gay male therapist whose partner died of AIDS may feel intense rage at a client who uses crystal methamphetamine and casually has unprotected sex with multiple partners when he goes on drug binges. It is important to remember that even LGBT clinicians may have strong reactions toward LGBT patients that can adversely affect their ability to view their clients objectively and treat them appropriately. It is crucial for all clinicians – heterosexual, gay, lesbian, bisexual, and transgendered – to fully examine their own beliefs and prevent them from affecting their clinical judgment.

129.2.3.4 Ideal Characteristics of Clinicians Working with the LGBT Client

A heterosexual clinician is not necessarily any less able to treat LGBT clients than a sexual minority clinician. As an analogy, consider a woman seeking an oncologist to treat her breast cancer. A good oncologist does not need to have had breast cancer herself to treat a breast cancer patient well. Rather, the patient will feel well cared for if the physician is knowledgeable, caring, empathic, and able to listen well to what the patient is saying. While having breast cancer certainly gives the physician a profound insight into the patient's experience, it does not guarantee that she is more knowledgeable or clinically sensitive. She might see her way of dealing with her own cancer as the only sensible coping method, which might make it more difficult to hear when the patient tells her that she needs to cope in a different way. Rather than focusing on finding a clinician who has had the exact same experiences, it is more productive to consider some general guidelines that should apply to all clinicians, regardless of sexual orientation or gender identity.

A good clinician should be reasonably free of homophobia, transphobia, and heterosexism. Because we all grow up in a heterosexist society, it is arguable that no individual is completely free of homophobia. However, a good clinician should have overcome most of these feelings and beliefs and should be aware of remaining homophobic, transphobic, and heterosexist ideas so that they do not interfere with treatment.

A good clinician should have an accepting and supportive attitude toward LGBT people. A crucial component of all clinical care is the positive regard for the client. Without this, the client cannot fully benefit from the treatment, and in substance abuse treatment, lack of positive regard can worsen a person's emotional life and substance use.

A good clinician should welcome and promote openness about sexual orientation and gender identity in the therapeutic setting. If a client is unable to disclose primary life issues to the clinician, then little therapeutic work can be accomplished. Additionally, welcoming openness about sexual orientation and gender identity fosters self-acceptance, which is a common difficulty for people with substance abuse issues.

While it is not essential that a clinician shares the same life experiences as the client, it is helpful for a clinician to be familiar with many of the issues commonly faced by LGBT people. Examples include the coming out process; dealing with heterosexism, homophobia, and transphobia; social isolation and stigma; and HIV and AIDS. Not all clinicians, even LGBT clinicians, will have an in-depth understanding of all of these concerns, but the clinician should be open-minded and willing to learn about unfamiliar issues and to understand them from the client's perspective.

Lastly, a good clinician should refrain from making assumptions of any kind and should actively listen for what the client identifies as his or her major life issues and goals, which may differ from the therapist's personal beliefs. The clinician should be able to actively listen to the needs identified by the client.

129.2.4 Selected Drugs with Particular Significance in the LGBT Community

While LGBT people are susceptible to abuse and dependence on all drugs and alcohol, there are a number of drugs that have particular appeal to members of the LGBT community, with a pattern of use distinct from the general population. Because the majority of research on substance abuse with LGBT people is from North America, this chapter is only able to describe drugs used in this community. Selected drugs used by the LGBT community in North America are described in the table below as an example of how the specific effects of different drugs can appeal to certain people who face specific psychosocial stressors. These are provided as an example to assist in the understanding of the use and misuse of drugs in other LGBT communities, who face their own unique psychosocial challenges (Table 129.1).

Table 129.1 Selected drugs used commonly in the North American LGBT community

Drug Mechanism of action	Specific population of users	Appeal unique to the population	Problems associated with misuse
Amyl nitrate Causes vasodilation, hypotension, and "head rush"	Gay men	Euphoria Eases discomfort of anal intercourse Intensifies orgasm Used in dance clubs and during sex	Nasal congestions Headache Severe hypotension in combination with PDE-5 inhibitors, can result in myocardial infarction Possible impairment of immune function
Ecstasy (Methylenedioxymethamphetamine, MDMA, "Molly") Increases presynaptic cytoplasmic levels of serotonin, dopamine, and norepinephrine in the CNS; induces their release into synaptic cleft. Increased levels of serotonin cause release of oxytocin	Gay men	Euphoria, dramatic increase in feeling of bonding with others, combating feelings of social alienation and isolation caused by homophobia Used at dance clubs, where it induces a feeling of belonging, connectedness, and community	Crash can involve severe depression, suicidal ideation, anxiety, panic attacks, and cognitive dysfunction. Other possible toxic effects include hypertension, hyperthermia, dehydration, hepatotoxicity, neurotoxicity, renal toxicity, and long-term cognitive impairment
GHB (gamma-hydroxybutyrate) GABA agonist; increases levels of serotonin and dopamine; mu opioid receptor agonist. Strong CNS depressant	Gay men	Decreases anxiety and inhibitions; dramatically increases libido; calm euphoria Overcomes sexual inhibitions due to internalized homophobia, allowing sexual gratification Used at dance parties and in combination with stimulants, especially methamphetamine Used in dance clubs and during sexual intercourse	Somnolence; respiratory depression; coma, especially when in combination with other CNS depressants; decreased sexual inhibitions can lead to sex without condoms and transmission of HIV and other sexually transmitted infections

(*continued*)

Table 129.1 (continued)

Drug Mechanism of action	Specific population of users	Appeal unique to the population	Problems associated with misuse
Methamphetamine (Meth, crystal, Tina, ice, crank, yaba) Increases presynaptic levels of dopamine and induces release of dopamine into the synaptic cleft in the CNS	Gay men	Dramatic increase in libido overcomes sexual inhibitions due to internalized homophobia, allowing sexual gratification Helps gay men with HIV to cope with their illness, reversing some of HIV symptoms, elevating mood and reversing depression during period of drug use	Extremely addictive, requiring more intensive treatment than other drugs. Sexually disinhibiting and commonly leads to anal intercourse without condoms, with transmission of HIV and other sexually transmitted infections. Crash can involve severe depression, suicidal ideation, anxiety, panic attacks, and hypersomnolence. Intoxication can cause anxiety, psychosis with paranoid ideation and tactile, visual, and auditory hallucinations. Frequent use leads to neurotoxicity of dopaminergic neurons, with resulting cognitive dysfunction and problems with behavioral inhibition due to decreased prefrontal cortical function. Other toxic effects include tachycardia, hypertension, myocardial infarction, arrhythmias, and stroke
Physique enhancing drugs: anabolic steroids Testosterone, stanozolol, oxandrolone, trenbolone enanthate, nandrolone decanoate; human growth hormone; human growth hormone-releasing peptide	Gay men	Increasing lean muscle mass, developing "hypermasculine" physiques that combat feelings of masculine inadequacy due to internalized homophobia	Psychological dependence on anabolic steroids to maintain positive self-esteem, with associated body dysmorphic disorder. Other side effects include excessive libido, aggression, irritability, explosive temper, testicular atrophy, gynecomastia, hypertension, hyperlipidemia, cardiomyopathy, hepatitis, polycythemia, and cellulitis at injection site

"Street hormones" Hormones purchased on the street for the purpose of cross-gender hormone treatment Includes testosterone, spironolactone, tamoxifen, synthetic estrogens, progesterone, and others	Transgendered people (both male and female)	Allows transgendered people who are disenfranchised and alienated from the general population's medical system to assist them in achieving a body more consistent with their internal gender identity. Cross-gender hormones are not considered drugs of abuse. However, street hormones are included here because their use without medical supervision can lead to multiple medical problems. Many transgendered people have been actively discriminated against or mistreated in the mainstream medical system, causing a general mistrust of the medical establishment by the transgendered community	Mood changes, including depression, irritability, aggression; nausea; edema; headache; hypertension; deep vein thrombosis and pulmonary embolism with smoking; hepatotoxicity; pancreatitis; endocrine dysfunction, including hypercortisolemia and hyperaldosteronism; deep tissue infections at injection sites; transmission of HIV, hepatitis B and C from sharing needles

129.3 Conclusion

This chapter provides an overview of the epidemiology of substance use disorders in the LGBT community in North America, as well as the particular psychosocial issues that increase the risk of substance abuse or dependence, as some of these individuals attempt to cope with these stressors by using the maladaptive tool of drugs and alcohol. Through data collected about this population over the past few decades, it becomes clear that it is neither sexual orientation nor gender identity per se that increases the risk of substance use disorders. Rather it is the social challenges that these individuals face, such as discrimination, harassment, assault, lack of social or legal protection, and lack of equality with mainstream society that cause anxiety, depression, internalized homophobia, and internalized transphobia.

Because this chapter presents information that is limited to North America, it may not accurately describe the situations that LGBT people face in other countries or the rates of substance use and abuse in those LGBT communities. It is important to acknowledge the many differing views of LGBT people, which may pose different challenges that LGBT individuals face in each country. Therefore, it is important for individual clinicians in each country to examine how their particular cultures view homosexuality and transgendered people, what the local laws are with regard to these people, and how these people may face social rejections, harassment, discrimination, assault, imprisonment, or even death sentences. Clinicians should listen to their LGBT patients with open minds to learn what their specific experiences are and use them as guides as to how to provide rational and compassionate care and treatment of addictive disorders.

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Addictions in Physicians: An Overview

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Abstract

Doctors are at high risk for developing addictive behaviors due to their easy access to self-treatment and because they are usually reluctant to ask for help when they feel mentally or emotionally distressed. Alcohol dependence and sedatives and/or minor opioid dependences are the most prevalent substance use disorders (SUDs) among physicians. However, when doctors come to accept treatment in programs specifically designed for them (Physicians' Health Programs), they show better outcomes than the general population.

The aims of this chapter are (a) to provide a brief comprehensive review of addictions in physicians, (b) to analyze the barriers that prevent doctors with SUDs from seeking help, (c) to give some keys to enhance early detection of affected individuals, (d) to explain the different strategies developed by Physicians' Health Programs, and (e) to describe the treatment principles that should be considered when treating physicians with addictions.

130.1 Introduction

The concern for the high rates of alcoholism and drug addiction among physicians traces back to 1869, when physician-educators started to be concerned for students and fellow practitioners addicted to alcohol, cocaine, or morphine (Brewster 1991). In the last decades, growing evidence has shown that doctors and other health professionals are at high risk for developing addictions, mainly substance use disorders (SUDs) (Talbott and Martin 1986; Flaherty and Richman 1993; McLellan et al. 2008; Dupont et al. 2009).

Physician impairment refers to those situations where physicians are rendered unable to carry forward their professional responsibilities adequately due to a variety of health issues, including a medical disease, psychiatric problems, substance use disorders, or dual diagnosis (O'Connor and Spickard 1997). Physicians' impairment due to addictive behaviors may be episodic or steady, leading to psychosocial deterioration and, finally, becoming dangerous both to the physician's well-being and their patients' safety (O'Connor and Spickard 1997; Lusilla et al. 2008; Dupont and Skipper 2012).

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The prevalence of addictions among doctors is said to be similar to that of the general population. Therefore, an estimated 10–14 % of physicians may become chemically dependent at some point in their careers (Flaherty and Richman 1993). Although physicians are less likely to experiment with illicit substances (such as marijuana, cocaine, and heroin), they are more prone to the use of alcohol and self-prescription of controlled medications such as benzodiazepine tranquilizers, minor opiates, and/or stimulants (Flaherty and Richman 1993; McGovern et al. 2000; Hughes et al. 1992; McLellan et al.2008; Skipper et al. 2009). Prescription substances are mainly used for self-treatment, whereas illicit substances and alcohol may be taken for recreational purposes mostly (Hughes et al. 1992), although the self-medication hypothesis cannot be disregarded.

Early diagnosis is critical because physicians are reluctant to ask for help when suffering from mental disorders (Stanton and Randal 2011), and their colleagues are often hesitant to intervene (Marshall 2008). Tendency to intellectualize psychiatric symptoms, greater stigma associated with mental disorders among doctors, and easy access to self-treatment with drugs, added to specific individual risk factors, may account for this increased risk (Firth-Cozens 1997; Hughes et al. 1992; Boisaubin and Levine 2001; Carinci and Christo 2009).

Doctors who delay seeking treatment frequently attempt to treat themselves (Hem et al. 2005a; Lusilla et al. 2008), potentially complicating their prognosis (Hughes et al. 1992), increasing the risk of developing comorbid conditions (Hem et al. 2005a), causing greater morbid-mortality (Lusilla et al. 2008), and usually leading to malpractice behaviors (Herrington and Jacobson 1982; Talbott and Martin 1987; McLellan et al. 2008; Skipper et al. 2009).

Dual diagnosis is a frequent condition associated with the risk of self-treatment. The combination of affective and alcohol disorders is the most common form of psychiatric comorbidity within physicians (Gastfriend 2005; Lusilla et al. 2008). Some Type II Personality Disorders, such as the Narcissistic and/or the Antisocial types, are often comorbid in physicians treated within specific programs for doctors once treatment has become compulsory (Angres et al. 2003). In nonpunitive programs (Lusilla et al. 2008), not only antisocial traits but avoidant and obsessive-compulsive ones are also present in doctors suffering from addictive disorders. However, specific occupational factors could play a role in the development of addictions in doctors: stressful situations, work-home time balance difficulties (with subsequent family stress), conflicts with patients, injury or accidents at work, life-and-death decisions, etc. (Marshall 2008; Carinci and Christo 2009).

Increased suicidal risk has also been associated with the presence of addictions and dual diagnosis in doctors (Center et al. 2003; Hem et al. 2005b; Lusilla et al. 2008). The typical physician at risk for suicide would be a man or a woman, around 50 years old, white, living alone, and suffering from one or more of the following conditions: depression, alcohol dependence, or any disabling medical condition (Center et al. 2003).

Therefore, addictions in physicians cause a serious concern due to their potential impact on patients' safety, the lives and careers of the impaired physicians, and the socioeconomic burden of the health-care system as a whole (Talbott and Martin 1986;

Boisaubin and Levine 2001; Dupont and Skipper 2012; Braquehais et al. 2012). However, if they come to accept treatment at programs specifically designed for them (such as Physicians' Health Programs, PHP), doctors with SUDs would have better outcomes and recovery rates in comparison to the general population (Herrington and Jacobson 1982; Carinci and Christo 2009; Dupont et al. 2009).

The majority of PHP are persecutory in nature, as their main aim is to protect population from the consequences of malpractice behaviors. Therefore, they look forward to warranting abstinence and mental stability but do not provide themselves clinical support and treatment for their patients. That is why some PHP, such as the Spanish program, were created to balance this secure approach with a clinical effort to prevent and treat conditions that may lead to malpractice issues.

The aims of this chapter are (a) to provide a brief comprehensive review of addictions in physicians; (b) to describe the usual barriers that prevent doctors with addictions from asking for help; (c) to give some keys to enhance early detection of affected individuals; (d) to explain the different strategies developed by specialized programs (PHP) in order to be able to deal with this problem, with a special focus on the new model for sick doctors developed in the Spanish PHP; and (e) to describe the main treatment principles that should be taken into account when treating physicians with addictions.

130.2 Addictions in Physicians

Boisaubin and Levine (2001) point out that medical students, like their peers outside medicine, may be fascinated by drugs and, during their early medical training, tend to overestimate their understanding of pharmacology and underestimate, or fail to comprehend, what addictions really mean. They may even continue to use drugs throughout medical school and into residency. Some physicians also begin using benzodiazepines and opiates during their residency training, when they first receive prescribing privileges. Most of them use those drugs to relief stresses generated during that time period (e.g., fatigue, early responsibilities, professional disillusionment, lack of emotional support, and less time to spend with friends and family).

College students may also use stimulants as "performance enhancers" or for pleasure (Arria and DuPont 2010). When comparing medical students to residents, Hughes et al. (1992) found that more residents reported lifetime usage of benzodiazepines (22.7 % versus 19.6 %) as well as barbiturates (8.5 % versus 7.3 %), but fewer of them reported cocaine use (29.2 % versus 32.5 %). With regard to alcohol use disorders, Flaherty and Richman (1993) found that 20.3 % of medical students met criteria for alcohol abuse or dependence in the 12 months prior to the interview.

Hughes et al. (1992), in a mailed survey to 9,600 physicians affiliated to the American Medical Association, reported that practicing physicians were as likely to have experimented with illicit substances in their lifetime as their age and gender

peers in society, but less likely to be current users of illicit drugs. Physicians' use of prescription substances (e.g., benzodiazepines, barbiturates, minor opiates, or amphetamines) was primarily related to self-treatment, while the higher prevalence of alcohol use could be related to their higher economic status. Schneider et al. (2007) also reported that Swiss primary care physicians tended to self-medicate with analgesics and tranquilizers.

In a nationwide, prospective, and longitudinal study following young Norwegian physicians from internship through the subsequent 9 years, Hem et al. (2005) found that physicians self-prescribed not only antibiotics (71–81 %) or contraceptives (24–25 %) but also analgesics (18–21 %) and hypnotics (9–12 %). Those suffering from mental disorders used mainly sedatives or hypnotics as a form of self-treatment.

With reference to medical speciality, the reported prevalence of alcohol use disorders and/or other addictive diseases in physicians is higher for psychiatrists (14.3 %) and emergency medicine physicians (12.4 %) compared to other specialities (Hughes et al. 1992). Psychiatrists are more likely to have used benzodiazepines (Hughes et al. 1992) and are also overrepresented in another study with alcoholic doctors (Bisell and Jones 1976). Hughes et al. (1992) also found that general practitioners and obstetric/gynecology physicians were more prone to use minor opiates, while anesthesiologists, emergency doctors, and chronic pain physicians used to self-prescribe major opiates. The trend was found to be similar within residents. Findings about anaesthesiologists have been also replicated in other studies (Garcia-Guasch et al. 2012). Although they are more likely to enroll US PHP because of opioid abuse, they have excellent outcomes similar to other physicians when they come to accept treatment at PHP (Skipper et al. 2009). In a recent study (Buhl et al. 2011), surgeons were found to be more likely than nonsurgeons to enroll in PHP because of alcohol-related problems but less likely to be admitted because of opioid use. They also had positive outcomes similar to those of nonsurgeons.

With regard to mandatory treatment, McLellan et al. (2008) reviewed the laboratory and medical records of 904 physicians admitted to 16 PHP in the United States (US). Five specialities represented more than 50 % of physicians: family medicine (20.0 %), internal medicine (13.1 %), anesthesiology (10.9 %), emergency medicine (7.1 %), and psychiatry (6.9 %). Alcohol use disorders and opioid abuse and dependence are the most frequent conditions among physicians compulsory referred to PHP programs (Brewster et al. 2008). In programs where physicians can also be admitted after self-referral, such as the Barcelona Substance Use Disorder Program, a higher prevalence for alcohol (83.3 %) and benzodiazepine (37.5 %) use disorders was found.

Smith (2008) underlined that most developed countries had shown a steady decline in physicians' smoking rates in the last decades. The lowest smoking prevalence rates (less than 10 %) have been consistently documented in the United States, Australia, and United Kingdom (Smith 2008; Smith and Leggat 2008). However, physicians in some developed countries and newly developing regions still appear to be smoking at high rates (Smith et al. 2008). In Catalonia, 24.5 % of working physicians continue smoking tobacco (Rohlfs et al. 2007).

130.3 Barriers to Ask for Help

Stanton and Randal (2011) identified some psychosocial factors that prevent physicians from asking help, increasing the risk of developing mental disorders: (a) doctors share a culture of unrealistic expectations, see themselves as super-people, and to show vulnerability has been identified with the risk of losing respect from peers and seniors; (b) these unrealistic expectations are associated with denial and minimization of need for self-care, personal vulnerability, and early signs of illness; (c) doctor colleagues, friends, and partners, whether recruited as doctor patients, doctor contacts, or treating psychiatrists, describe experiences of considerable difficulty in identifying concerns and speaking about them to other doctors; and (d) nondoctor personal contacts describe them as being unable to identify difficulties and speak about them.

Some other factors may increase this inability to develop healthy coping strategies (Firth-Cozens 1997; Rakatansky 2005): high self-criticism; low self-esteem; poor bonding to relatives; competitive, humiliating, and status-conscious work environment; and burnout symptoms related to high job demands.

Easy access to self-prescription may lead to tolerance and dependence of some licit drugs, while alcohol use may become a "socially accepted" strategy to deal with stressful situations. Once the addiction pattern is established, it gets even more difficult for the sick doctor to ask for help.

In fact, a high proportion of doctors show inadequate attitudes toward their general health care (Bruguera et al. 2001; Hem et al. 2005a). As some doctors with addictions do not ask for help, some direct or indirect signs (O'Connor and Spickard 1997; Boisaubin and Levine 2001) may help their colleagues identify their problem (see Table 130.1). In fact, it is the physician's ethical responsibility to

Table 130.1 Identifying physicians with SUDs

Indirect signs	Abnormal behavior
	Loss of reliability
	Unjustified absences from work
	Frequent medical complaints
	Abnormal prescription (tendency to self-prescription)
	Mood changes
	Isolation from colleagues
	Staff concerns of one colleague's behavior
	Citations for impaired driving
Direct signs	Smell of alcohol
	Somnolence
	Hyperactivity
	Disinhibition
	Ataxic gait
	Slurred speech
	Tremor
	Disheveled appearance
	Depressed mood

identify alcohol-impaired or drug-impaired physicians in order to help them return to optimal functioning and to safeguard the health of patients from the care of impaired physicians (O'Connor and Spickard 1997; Boisaubin and Levine 2001).

130.4 Treatment

130.4.1 Physicians' Health Programs

Specialized programs to help doctors who are dependent on substances seem to provide the best available measures for protecting patients and for recovering physicians' careers and well-being (Carinci and Christo 2009) (Table 130.2).

First PHP were developed in every US state since the late 1970s in order to identify and treat sick doctors who had a misconduct as a consequence of a mental disorder – mainly, addictions (Talbott and Martin 1986; Dupont et al. 2009; Dupont and Skipper 2012). The US Federation of Physician Health Programs (FSPHP) offers state programs (44 states are full members, as membership is voluntary), regional and national meetings, as well as electronic forums for issues concerning physicians' health (Dupont et al. 2009). US PHP contracts offer support and temporary safe haven for physicians who are typically in jeopardy or under pressure from others due to problems related to addictions. All US programs maintain a close relationship with the physician-as-patient state medical licensing boards. In fact, the boards often accept the care of the sick doctor instead of imposing disciplinary actions for them. Most contracts stipulate intense, ongoing treatment with substance monitoring, together with a close supervision plan (Dupont et al. 2009).

Table 130.2 Physicians' Health Programs (PHP)

Location	PHP
US	Physician Health Programs (44 states)
Canada	Physician Health Programs (4 provinces)
	Physician-Family Support Programs (4 provinces)
	Physician at Risk Program (1 province)
	Professional Assistance Program (1 province)
Australia	Doctors' Health Advisory Services-Support programs (6 states)
	Physician Health Program (1 state)
Europe	UK: Doctors for Doctors (BMA), Doctors Support Network, Practitioner Health Program (NHS), Sick Doctors Trust
	Switzerland: ReMed
	Norway: Research Studies (NMA) and Villa Sana Resource Center
	Spain: Physician Health Program (PAIME) and Evaluation Unit, Preventive Programs and Research Studies (Galatea Foundation)

BMA British Medical Association, *NMA* Norwegian Medical Association

Similar PHP were developed later in every Canadian province (Puddester 2004; Brewster et al. 2008). Other programs were developed in Australia (Jurd 2004) and the United Kingdom (Oxley 2004), trying to improve strategies to reach sick doctors and prevent those conditions, promoting healthy lifestyles among physicians, and offering counseling when needed. Norway, Austria, and Switzerland developed similar basic preventive and counseling services for doctors. Other European countries are receptive to these initiatives and plan to create similar programs in the future (e.g., in France some regions have created their own PHP).

On the other hand, cross-country collaboration is critical when promoting doctors' well-being. The American Medical Association (AMA), the Canadian Medical Association (CMA), and the British Medical Association (BMA) organize each year the International Conference on Physician Health to increase awareness on the topic and enhance networking activities. The European Association for Physician Health (EAPH) is a network of European groups and individuals concerned with doctors' health that regularly meet to (a) share the expertise and good practice on the treatment of doctors by doctors, (b) influence and encourage the development of health services for doctors, and (c) undertake joint research on the health and well-being of doctors.

Most programs include prevention strategies to increase awareness of the problem both among medical students and doctors as well as promoting their integral well-being. Promoting healthy coping strategies to deal with stressful situations and overcoming doctors' barriers to ask for help when they suffer mental disorders are the main objectives of prevention campaigns for this professional group.

In summary, national and international strategies are needed to sensitize medical students, residents, and doctors to the dangers of self-treatment with controlled prescription substances, to enhance functional coping strategies among physicians, and to develop specific PHP to treat doctors who finally develop addictive disorders.

130.4.2 Key Factors to Treat Doctors with SUDs

As already mentioned, physicians have a good response to addiction treatments when compared to the general population. Reports from several PHP report long follow-up abstinence rates for physicians to be around 70–80 % (Boisaubin and Levine 2001; Brewster et al. 2008; McLellan et al. 2008; Dupont et al. 2009).

Brewster et al. (2008), after monitoring 100 physicians with addictions treated at the Ontario PHP during 5 years, found that 71 % had no relapse and a total of 85 % successfully completed the program. Sixty-six percent had been compulsory referred by their College of Physicians, and 16 % had been sued for malpractice behaviors.

McLellan et al. (2008) retrospectively analyzed the laboratory and medical records of 904 physicians admitted to 16 PHP in the United States. At 5-year follow-up, 78.7 % were licensed and working. The typical program consisted of two stages: formal treatment (inpatient and outpatient treatment) followed by supervision after treatment. Most patients (78 %) entered inpatient treatment followed by outpatient treatment.

The rest of physicians (22 %) went directly to outpatient treatment. Those with good compliance and positive progress were eligible to return to work under supervision about 6 months after the start of treatment. Physicians were expected to attend Alcoholics Anonymous or other 12-step groups (92 %) during their recovery period. Urine testing was carried out four times a month early in care, tapering to one or two times a month throughout the monitoring period. The frequency of testing was contingent on the results of urine analysis and on the results of the supervision care plan. Urine testing was generally observed by the responsible staff (75 % of urine samples). The typical testing panel covered 20 substances (amphetamines, barbiturates, benzodiazepines, opiates, several opiates, cocaine, cannabinoids, and ethyl alcohol). Some cases needed to be tested using the hair (0.2 %), saliva (0.1 %), and breath (0.6 %).

US PHP programs complete the integral treatment group therapy and support group attendance at 12-step programs such as Alcoholics Anonymous, Narcotics Anonymous, and/or Caduceus (i.e., a program specifically designed for impaired doctors) (Carinci and Christo 2009).

In summary, results of follow-up studies support the need for and the efficacy of highly specialized programs for physicians with addiction problems (Boisaubin and Levine 2001; Carinci and Christo 2009; Dupont and Skipper 2012).

Some keys to success (Talbott and Martin 1986; Dupont et al. 2009; Dupont and Skipper 2012) when treating those doctors are (see Table 130.3):

1. Offering immediate and highly confidential intervention. Providing an adequate, easy-access, and confidential treatment as soon as the sick doctor seeks help is critical.
2. Evaluation and triage at the appropriate facility where a comprehensive case management is offered. Treatment at outpatient or inpatient facilities will depend on the severity of their addictive disorder.
3. The treatment staff should be trained to deal with the particular occupational components and with the most common defense mechanisms of the impaired physician.
4. Addictions must be conceptualized as mental disorders. Careful presentation of the diagnosis and the dynamics are critical to the acceptance of the "disease model" by physician-as-patients.

Table 130.3 A decalogue to treat doctors with SUDs

1. Immediate response and highly confidential treatment
2. Specialized treatment setting
3. SUD conceptualized as a mental disorder under a biopsychosocial paradigm
4. Specifically trained staff
5. Peer-group therapy
6. Uninterrupted and long follow-up program
7. Frequent random drug testing
8. Family involvement
9. Appropriate reentry into practice when maintained abstinence
10. Advocacy and relapse contingency plan

5. Peer-group therapies and mirror image techniques are useful in breaking through denial and overcoming the physicians' barriers to ask for help.
6. A non-interrupted, long follow-up program with extensively monitored and structured aftercare component is a key factor to foster physician recovery.
7. Random drug testing is a key component of adequate monitoring. Failure to call in for randomization is a prognostic indicator of imminent relapse.
8. Family involvement. Psychoeducation with families and significant others as well as family therapy when needed should be part of the patient-tailored treatment.
9. Appropriate reentry into practice when the impaired physician remains abstinent should be warranted. Supervision at work may become necessary in some cases.
10. Advocacy and a relapse contingency plan must be implemented when needed.

130.4.3 A New Model for Sick Doctors: The Spanish PAIME

In 1998, the Integral Care Program for Sick Doctors (PAIMM, in Catalan, and PAIME, in Spanish) was created in Barcelona (Spain) by the Regional Health Department of Catalonia (Spain) and the "Colegio Oficial de Médicos" of Barcelona (Bosch 2000), an institution similar to the Board of Trusties in Anglo-Saxon countries. Later on, it extended its activity to other "Colegios Oficiales de Médicos" all over Spain. The institutions called "Colegio de Médicos" act both as Board of Trusties and Medical Associations, thus being responsible for warranting safe medical practice in Spain.

The PAIME's main aim was to prevent and treat mental disorders in physicians and help them go back safely to their professional practice. The PAIME, in contrast with other international programs, was inspired by a new philosophy regarding the approach to the "sick doctor" phenomenon as it intended to become a highly confidential, non-persecutory, nonpunitive, voluntary, therapeutic, and recovery-oriented program. Treatment becomes mandatory only when there is a risk or evidence of malpractice behaviors.

In order to warrant confidentiality, a new name is given to each patient entering the program (e.g., all patients' last names are changed in order to warrant anonymity). Real identity data are only disclosed in circumstances where risk for the SD or others is involved (Table 130.4).

Table 130.4 The Spanish model (PAIME): a new approach to physicians' well-being

New philosophy	**Highly confidential**
	Only mandatory treatment when risk or evidence of malpractice
	Non-persecutory
	Voluntary access
	To promote rehabilitation ("regain good professionals")
	To enhance prevention

Therefore, the philosophy of the PAIME appeared in the international scenario as a new approach to doctors' mental health where the emphasis was put on enhancing voluntary help seeking among physicians suffering from mental disorders and promoting the return to their professional practice in good conditions. Their founders believed this approach would certainly help SD not feel punished or prosecuted when having mental disorders and, therefore, enhance help seeking among them (see Table 130.3).

All PAIME units in Spain have outpatient facilities where psychiatric and psychotherapeutic treatment is provided to all SD registered at their "Colegios de Médicos." PAIME units also warrant mandatory follow-up surveillance and treatment for those cases in which risk or evidence of malpractice issues can be involved. The PAIME unit in Barcelona, the Galatea Clinic, located in the mountains of the northern part of the city, has inpatient and outpatient facilities where psychiatric and psychotherapeutic treatments are provided to SD. It is the psychiatric hospitalization unit where SD from the rest of PAIME units in Spain are referred to if they need inpatient treatment (Table 130.5).

Since 2008, the Galatea Clinic offers a new highly structured, patient-tailored program in which a combination of psychopharmacological treatment and psychotherapy for doctors with SUDs is provided.

After a 1-month day-hospital daily intensive phase, all patients from Barcelona enter a 2-year follow-up stage where controlled, random drug screening, weekly motivational group therapy, and regular psychiatric and psychotherapeutic evaluations take place. Our psychotherapeutic approach combines both cognitive-behavioral techniques and motivational interventions as they have proven to be highly effective in alcohol and other SUD (Kilmas et al. 2013). A retrospective, longitudinal, cohort study was carried out over 2 years, from 1 February 2008 to 1 February 2010, of 153 medical records of physicians and nurses admitted to the

Table 130.5 Barcelona clinical unit (Galatea Clinic)

Highly structured intervention programs	Evaluation unit
	Substance use disorders program
	Mental disorders program
Treatment facilities	Psychiatric inpatient unit
	Outpatient facilities
	Day hospital
Treatment modalities	Psychopharmacological treatment
	Individual psychotherapy
	Group psychotherapy
	Family intervention
	Physical examination
	Neuropsychological assessment
Target patients	Residents
	Practicing physicians

program. During this 2-year period, only 15.7 % (54.2 % men and 45.8 % women) of all patients were readmitted after relapse. Of the readmitted patients, 54.2 % suffered from another mental disorder, mainly major depressive disorder (25 %).

The PAIME unit in Barcelona has treated up to 2,000 physicians so far, and the Galatea Clinic intends to promote their activity overseas, offering their expertise and specialized treatment to SD coming from all around the world. When the program started, more than a decade ago, most patients were referred for malpractice issues; nowadays, most patients are self-referred, and up to 85–90 % are able to go back to their professional practice in good conditions after their treatment process.

130.5 Conclusion

As SUDs in physicians may lead to serious consequences both for the physicians-as-patients and for their safe practice, most PHP only offer mandatory treatment to sick doctors. At the same time, although physicians are usually reluctant to ask for help, when they accept to be treated at confidential, highly structured, long-term programs, specifically designed for them, they have better outcomes, showing recovery rates higher than the general population. The Spanish Integral Care Program for Sick Doctors was created not only to warrant safe practice (through compulsory treatment when needed) but also to enhance voluntary help seeking among physicians. This new philosophy may be of greater help for addicted doctors instead of the standard mandatory treatments provided by other specialized programs.

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Substance Use in Populations Displaced by Conflict

131

Nadine Ezard

Contents

Abstract

Around 45 million people are displaced by conflict; the majority have been displaced for around two decades. Conflict-displaced populations suffer excess mortality from communicable and noncommunicable diseases. Substance use is increasingly recognized as an important underlying behavior and determinant of these diseases and has been documented from a range of displaced populations: refugee and internally displaced, in and out of camps, and urban and rural settings, in Africa, Asia, Europe, and South America. The literature mentions a variety of substances, including alcohol, amphetamine-type stimulants, benzodiazepines, cannabis, and opiates. (Weak) data suggest an association between male gender, older age, multiple traumatic episodes, and increased substance use in displacement. Transitions in patterns of substance use appear to reflect a combination of pre-displacement patterns, host population patterns, and substance availability. Theoretical models suggest that psychological distress, social stressors, changes in social norms and networks, and growing

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poverty and inequality may underlie these transitions. Harm related to substance use is well documented among non-displaced populations; documented problems specific to displaced populations include injection-related infection risks, mental health problems, suicide, and intimate partner violence. Conflict is a social determinant of health and an important influence on the distribution and patterns of substance-related harm globally. Interventions to reduce substance-related harm among populations displaced by conflict should be multilevel and multisectoral. Individual interventions target those who are already at risk of or experiencing harm; structural interventions address the underlying social determinants of substance-related harm. More study of intervention effectiveness is needed.

131.1 Introduction

The world's population is increasingly mobile, and conflict is an important cause of population mobility. In 2012 there were around 45 million people displaced by conflict (United Nations High Commissioner for Refugees 2013). The majority are from conflicts in Africa, Asia, and the Middle East and remain within those regions; two thirds are displaced within their own countries and not entitled to international legal protection afforded to refugees. Although many displaced people live in camps or collective settings, most are hosted among non-displaced populations, and more than half live in urban settings. New crises cause acute onset displacement, yet the majority of displaced people have been so for decades. Around two thirds of refugees are in so-called protracted situations of more than 5 years' duration, and the average length of stay in displacement is now around 20 years (Internal Displacement Monitoring Centre 2013; United Nations High Commissioner for Refugees 2013; World Bank 2011).

The high death rates among conflict-displaced populations are mostly due to noncombat-related causes, a mix of communicable and noncommunicable illness. Substance use is an important underlying behavioral determinant. The association between substance use – particularly alcohol – and chronic illness, depression, and other mental health problems is well documented, as is the link with infections such as tuberculosis and HIV. Displaced settings provide contexts in which substance use may be promoted and in which substance-related harm may flourish. Economic, psychosocial, and cultural aspects of displaced contexts can promote newer and more hazardous patterns of substance use. Displacement causes a speeding up of the urbanization process and shifts to urban – and potentially more harmful – patterns of use.

This chapter will review the literature on substance use among populations displaced by conflict and the relationship between conflict-induced displacement and changing patterns of substance use. (This chapter is concerned with groups of displaced people, be they within or across international borders. It does not directly address onward migration or third-country resettlement, which

introduces different contextual factors.) It will then explore the literature on substance-related harm among populations displaced by conflict. By conceptualizing conflict as a social determinant of health, the chapter will conclude with an intervention framework for minimizing substance-related harm among these populations.

131.2 Key Concepts

- **Armed conflict:** According to international humanitarian law, war opposing two or more States is termed international armed conflict, and war between governmental forces and nongovernmental armed groups, or between these groups alone, is called non-international armed conflict (International Committee of the Red Cross 2008).
- **Internally displaced persons:** By convention, where persons are displaced within state borders due to armed conflict, they are termed internally displaced persons (IDPs) (United Nations Office for the Coordination of Humanitarian Affairs 2004).
- **Interventions:** Interventions are actions taken to prevent the onset, continuation, or deterioration of an adverse health outcome (often termed, respectively, primary, secondary, and tertiary prevention) and to promote positive health outcomes. Interventions can include services, programs, laws, regulations, and policies and may include the unintended health consequences of non-health sector policies and programs. Interventions can be classified as individual interventions, targeting individuals and their families, or structural, targeting the social environment.
- **Refugees:** According to international refugee law, people fleeing conflict and displaced across international borders by armed conflict are termed refugees. The legal definition of a refugee is someone who, "owing to a well-founded fear of being persecuted for reasons of race, religion, nationality, membership of a particular social group or political opinion, is outside the country of his nationality, and is unable to, or owing to such fear, is unwilling to avail himself of the protection of that country" (United Nations 1951: Article 1(A)2; 1967).
- **Social context:** Substance use patterns, problems, and solutions are all embedded in their social context, a term used to describe the cultural, social, and structural environment that shapes human behavior and health outcomes of behavior.
- **Social determinants of health:** Social determinants of health include living conditions across the life course – such as education, environment, and access to health care – and the underlying economic and political structures determining the distribution of resources and power (Commission on the Social Determinants of Health 2008).

- **Substance use:** The phrase "substance use" means ingestion of a medicinal, industrial, or plant-based psychoactive chemical with the aim of changing consciousness, mood, behavior, or thought processes. For the purposes of this chapter, tobacco products and nicotine are excluded. Substance use covers the spectrum of behavior from beneficial and nonproblematic to hazardous and harmful.

131.3 Substance Use in Displacement

Use of a number of different substances has been reported from displaced populations, depending on the local context and substance availability. Globally, alcohol use is the most prominent, its use documented from a range of settings, including camps in Croatia (Kozarić-Kovačić et al. 2000), Uganda, and the Thai-Burma border (Ezard et al. 2012) and among urban displaced in Colombia (Roberts et al. 2011). Khat use is very prevalent among the most conflict-affected areas of Somalia among combatants and civilians (Odenwald et al. 2007; Hansen 2010). Opiate and cannabis use is common among displaced populations in Pakistan and Iran (Ezard et al. 2011). Documented use of other classes includes amphetamine-type stimulants, cannabis, glue, and other inhalants.

Patterns of use also vary widely. These patterns can be characterized as an extension of pre-displacement patterns, transition to host patterns, or a mix of the two (Ezard et al. 2011). For example, frequent high-volume use of home-brewed alcohol has been documented among some men living in long-term conflict-displaced settings in northern Kenya, Uganda, and Thailand (see Box 131.1 for a case example). Refugees from Somalia in Ethiopia describe a transition in patterns of khat use from celebratory and weekend use to daily use (Hansen 2010). These patterns of use are considered an exaggeration and modification of pre-displacement use patterns.

On the other hand, new-onset use, mirroring that of the host population, can occur. This is the pattern observed among some Afghan refugees in Iran, who have adopted the use of Iranian *kerack* (a concentrated form of heroin) and *crystal* (a predominantly methamphetamine preparation). Transition to injection use of opiates among Afghan refugees in Iran, Pakistan, and Turkmenistan has been well documented; this practice was diffused into on return and is now normalized in Afghanistan (Todd et al. 2012). Figure 131.1 shows a diagrammatic schema for understanding changing patterns of use in displacement.

How and why these transitions occur is complex and poorly understood. There are a number of contributory elements, which act at both individual and social levels. Individual trauma experiences, for example, have been hypothesized to promote substance use. Among combatants, conflict exposure has been shown to result in increased substance use. Among conflict-displaced civilian populations, there is some (weak) evidence that multiple trauma exposure promotes substance use (Ezard 2012). It is not clear how much of this substance use is new-onset

Box 131.1. Case Study: Alcohol Use in Mae La Refugee Camp, Thailand, 2009

Armed conflict in Burma has displaced more than two million people into neighboring Thailand since independence from the UK in 1948. An assessment of alcohol use was conducted in Mae La refugee camp in 2009. More than 150,000 refugees lived in nine camps along Thailand's western border, in addition to 500,000 people displaced internally within Burma and several million migrant workers in Thailand. Mae La was the largest of the camps, established in 1984, with a population of around 45,000. The majority of the population was Karen, an ethnic minority in both Thailand and Burma, of Buddhist and Christian religions. The Karen people had been engaged in armed resistance against the Burmese state for a number of decades. Employment and education opportunities were limited, and the population was largely dependent on external aid. There was high population turnover and an active program of third-country resettlement.

A range of substances was used in the camp including opium, heroin, *ya ba* (Thai for "crazy medicine," a tablet form of methamphetamine mixed with caffeine), cannabis, benzodiazepines, other pharmaceuticals, and, among young people, glue sniffing. Alcohol caused the most public health and social concerns for the population, implicated in episodes of insecurity, gender-based violence, physical assault, and suicide. Around a quarter of men and no women of reproductive age screened positive for risky drinking. Prevalence of risky drinking was likely to be lower than many countries of resettlement and the host country, Thailand.

Beer, wine, and whisky could be obtained at nearby bars and shops, although not officially permitted to be sold in the camp. The most popular form of alcohol, however, was cheap, locally brewed rice liquor, despite its illicit status in Thailand. It was preferred only for reasons of affordability – no one claimed to enjoy the taste and many expressed fears around contaminants and a belief that production had moved away from traditional methods. "Auu! . . . you see they make with shoes as well as battery acid and other things which are not clean" said Naw W, a 34-year-old woman and long-term resident interviewed as part of the study (the names presented here are pseudonyms).

Alcohol had been used for many years in Karen culture for the purposes of socialization, and it was often referred to in Karen as "happy water." According to Saw S, a 42-year-old man who had been living in Mae La for 17 years, this meant "it is like we drink alcohol in order to make us happy . . . I have a lot of friends sometimes we buy a bottle of alcohol and drink together with friends."

Its use was subject to strong social controls. Saw S went on to explain that "[I] come back to eat after drinking, but I do not continue to have more. I just drink it in moderation." Small amounts of alcohol were considered "good to eat rice" (improve appetite) and "like medicine" (improve health). Intoxication, however, was proscribed. As Saw E, a 43-year-old man and long-term resident, explained: "[if alcohol is drunk] within limits, it is like medicine.

If it is over the limit, it is dangerous." One of these dangers was being loose tongued and indiscreet, described frequently as "the theft of the buffalo is revealed."

Use by women was also proscribed, and abstinence associated with femininity. Naw P, a 22-year-old woman who had been in Mae La since the age of 17, explained that "[men drink] because they get tired; they keep drinking until they are drunk in the street. Women also get tired! Drinking alcohol to freshen up that is just giving in to your desires." Saw Y, a 24-year-old man, thought that there were fewer women than men who drink because "women can control themselves if they get upset. Usually, men have no self-control," and Saw V, a 20-year-old man, thought that one reason women don't drink is because "they are afraid that the neighbors will gossip about them."

Nevertheless, there was a dominant belief that the pressures of displacement and refugee camp life were starting to erode these strong controls, and drinking norms were changing. Alcohol use was shifting from celebratory and occasional towards every day and high volume, at least by some people. A number of rationales were given to explain this. For example, Say, a 19-year-old man, described using alcohol as a form of self-medication to deal with distressing emotions; "I drink so that I don't need to think so much" he explained. Others described alcohol use to manage social stressors. Saw Y, a 24-year-old man explained, "Mae La residents have only alcohol. If they go out, the Thai will catch them. Here, it's like being in a farm. It is surrounded by a fence; they can't go out, so if they get upset, there's only alcohol to get release." He went on to list the constrained options for many people and the hopelessness that this engendered, "so they just drink alcohol."

For some, disruption to existing social hierarchies resulted in changes in controls on alcohol use behaviors. According to Saw P, a 56-year-old man who had been in out of the camp since it was established,

> now the UN also control as well as the Thai authorities so people do not know to who to listen to and parents have less power to take control over their children . . . Alcohol drinking is not unusual for the Karen people, the Karen people drink alcohol based on their custom such as weddings, funerals and so on . . . they drink alcohol in these situations but had no problems with alcohol drinking. But now people are creating problems and fighting due to alcohol drinking so it is frightening the lives of the people in the camp . . . but now more and more people are coming into the camp with different ethnic backgrounds and different characteristics and more fighting, more drugs, and more problems happen in the camp.

As a result of these social changes, alcohol use was becoming more prominent and more dangerous.

In addition, there was a belief that increased economic resources derived from third-country remittances enabled participation in the host country alcohol market. This promoted commercial alcohol consumption. Indeed the camp was not isolated from marketing efforts of alcohol companies in Thailand, one of the fastest growing alcohol markets in the world.

For example, sponsorship of the camp football team by a well-known beer manufacturer was evident.

Together these economic, cultural, and social transitions contributed to changes in alcohol use behaviors and norms and increased the potential of alcohol-related harm. Risky alcohol use was common among men but not women and warrants targeted early intervention. Nevertheless, the population may have been partially protected from rapid rises in problem alcohol use observed in the host country, Thailand.

Source: Ezard et al. (2012)

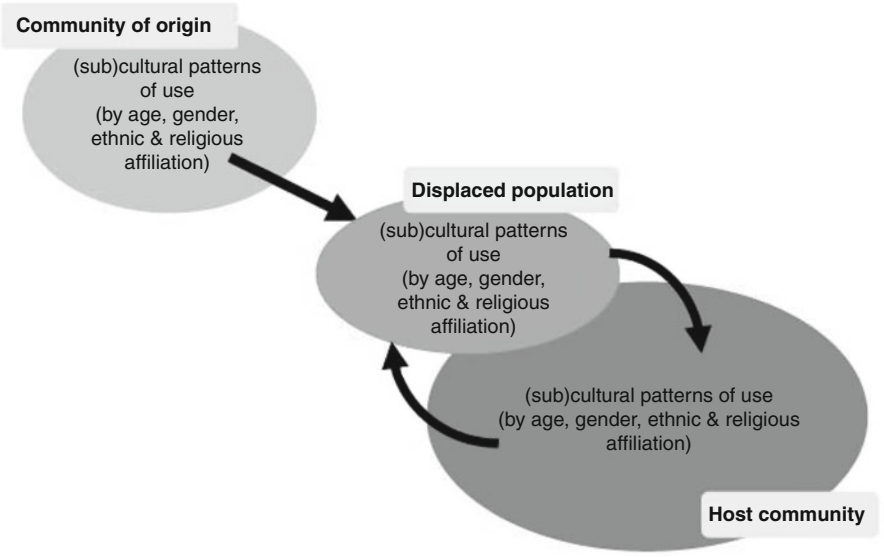

Fig. 131.1 Changing patterns of substance use in displacement (Source: Ezard et al. 2011)

following trauma or how much is increased use among those with preexisting substance use disorders. The relationship between formally diagnosed post-traumatic stress disorder and substance use is complex and is mediated by gender and pre-displacement substance use disorders (Kozarić-Kovačić et al. 2000). It may be expected that other mood disorders which are highly prevalent among conflict-displaced populations, such as depression and anxiety, may be associated with substance use as seen in non-displaced populations. Perhaps most importantly, a history of substance use disorder pre-displacement is likely to predispose an individual to substance use disorder following displacement. Individual socioeconomic determinants are also important. For example, homelessness, unemployment, and a lack of education are prevalent among opiate using Afghan refugees

in Pakistan (and more prevalent than among the non-displaced hosts) (Zafar et al. 2003).

Substance use patterns vary by gender – in general men use psychoactive substances more frequently and in greater amounts than women. For example, Roberts and colleagues showed that being older, male, and a history of exposure to multiple war-related traumatic events increased the odds of drinking alcohol at risky levels among displaced populations studied in northern Uganda (Roberts et al. 2011). One study from the Thai-Burma border suggested that women in a long-term refugee camp drank very little alcohol, whereas around a quarter of men drank at risky levels (Ezard et al. 2012). Nevertheless, women are not always excluded from participating in substance use. Afghan women in Pakistan reported commonly using opiates in one study (Ezard et al. 2011). An important proportion of women screened positive for alcohol dependence in a study from a Croatian IDP camp, a setting in which the prevalence of adult alcohol dependence was extremely high: 8 % of women and 61 % of men (Kozarić-Kovačić et al. 2000).

Supply factors will also influence observed patterns of substance use. Opiates, for example, are widely available and used among Afghani refugees, although believed to be less than among the host populations (Ezard et al. 2011). Grains supplied in food rations have been used to manufacture alcohol in long-standing displaced settings, such as refugee camps in Kenya and Thailand. Similarly transition to urban patterns of frequent heavy drinking – such as seen among some displaced populations – is believed to be stimulated by the more ready availability of alcohol (Room et al. 2002).

Economic drivers underlie these observed transitions. Alcohol brewing and sale is an important source of income in settings where other livelihood options are constrained – such as in among IDPs in camps in northern Uganda and refugees in Kakuma camp, Kenya (Ezard et al. 2011). Arguably this may contribute to the availability – and use – of alcohol. Transition to injection routes of administration such as observed among Afghan refugees in exile (Todd et al. 2007) is also partly driven by the microeconomy. Injection is more efficient, with greater psychoactive effect for the same amount of substance, and less easily detectable than smoking, important in a setting where the substance is illegal and the user may not be legally permitted in the country or subject to harassment from the authorities.

Various theoretical models can be applied to explain why substance use may be popular among populations displaced by conflict. The self-medication hypothesis (Khantzian 1985) proposes that psychoactive substances are used to relieve individual suffering, particularly among groups of people who are powerless and poor (Singer 2008). This hypothesis is shared by a number of displaced persons and observers. For example, research conducted among refugees from Sudan in Kenya explores the use of alcohol by refugees to manage thoughts of past trauma and the stress of confinement, hopelessness, and powerlessness (Ezard et al. 2011). Similarly research from refugees from Somaliland in Ethiopia describes increased khat use to moderate guilt and emotional trauma (Hansen 2010).

Alternatively, the social stress model suggests that disruption to relationships between people and social networks may induce fear and anxiety and promote substance use (Rhodes and Jason 1990). It is likely that these social changes represent more than just psychological stress. Displacement can disrupt tight family and community networks and social hierarchies and replace them with new, expanded, and unstable networks, removing preexisting social controls on substance use. Qualitative research conducted with refugees from Burma living in a long-standing refugee camp in Thailand explores how changing social structures influence changes in substance use (Ezard et al. 2012) (see Box 131.1). Altered norms emerge, accompanied by transition to potentially more harmful patterns of substance use (Friedman et al. 2006). Social norms are likely to be at least as important as social stressors in mediating substance use (Galea et al. 2007).

131.4 Harm Related to Substance Use in Displacement

A public health perspective focuses on the harm related to substance use rather than the substance use per se. Harm can include impacts on individual health or social functioning. The harm related to substance use is well documented: alcohol alone is associated with dozens of illnesses and is responsible for 4 % of global mortality (Rehm et al. 2009). In addition, a number of health and social problems associated with substance use have been documented to be of particular concern among conflict-displaced populations. These include communicable and noncommunicable diseases, violence, and economic impacts.

For example, higher HIV seropositivity and lower tuberculosis treatment success has been documented among people who inject drugs compared with people who do not inject drugs in a conflict-displaced population in India (Rodger et al. 2002). HIV risk behaviors – unsafe sexual and injecting practice – were more common among refugees than host populations in Pakistan (Zafar et al. 2003). A similar pattern was observed among displaced refugees returning to Afghanistan (Todd et al. 2007). Transition to injection may introduce HIV into communities. Molecular evidence from Afghanistan suggests a nascent epidemic of IDU-associated HIV infection in Herat, with a similar strain of HIV observed in Iran, where the majority of opiate injectors began injecting while refugees (Sanders-Buell et al. 2010).

Compounding the health risks of alcohol consumption, the livelihood imperative to generate income from alcohol production may promote the addition of harmful chemicals. Qualitative research from Mae La refugee camp in Thailand explored community perceptions that artisanal alcohol production process may be dangerous as a result of the introduction of poisonous additives (see Box 131.1). Similar observations have been made in long-standing camps in African contexts. Nevertheless, although deaths have been reported from contaminants such as methanol or herbicides in poorly produced alcohol, it is the amount of ethanol and pattern of consumption that pose the greatest threat to public health globally (Lachenmeier and Rehm 2009).

Other health problems include mental illness, which can be a cause or consequences of substance use. Among some displaced populations, substance use has made an important contribution to completed suicides. For example, alcohol has been implicated in the majority of suicides among war displaced in northern Uganda (Kinyanda et al. 2009).

Substance use has been implicated in other forms of violence. Intimate partner violence is common among women in conflict-displaced settings and is linked with substance use. In one long-standing refugee camp in Ethiopia, women whose male partners drank alcohol had twice the odds of experiencing intimate partner violence within the previous 12 months than those who did not (Feseha et al. 2012). Similarly in long-standing IDP camps in northern Uganda, women whose husbands use alcohol were 50 % more likely to report intimate partner violence (Annan and Brier 2010). This connection has been made for other substances too – for example, violence against women was linked with their male partners seeking money for cannabis in a qualitative study in Pakistan (Ezard et al. 2011).

Substance use has been observed to have important economic impacts at the individual, household, and community level. These aspects have not been explored in depth. Household expenditure can be considerable – in refugee camps along the Thai-Burma border, 80 % of households spent money on substances (Cardno Agrisystems 2009). Theft, family conflict, poverty, and child neglect among families with opium-dependent household members increased when the population was displaced away from traditional opium-growing areas in Laos (Westermeyer 1982). Collectively, transitions in substance use may contribute to the changing economic environment. Returning refugees to Somalia from Ethiopia promotes an increasingly thriving market, supported by third-country remittances (Hansen 2010). In turn, khat trade is believed to contribute to prolonging the conflict.

131.5 Intervention Framework

The literature review presented above suggests how conflict may drive changes in social conditions, which in turn may promote transitions in substance use and development of substance-related harm. Public health has long been concerned with understanding links between the context in which people live and the distribution of health outcomes. These social determinants include living conditions across the life course – such as education, environment, and access to health care – and the underlying economic and political structures determining the distribution of resources and power (Commission on the Social Determinants of Health 2008).

Conflict can be considered to be a social determinant of health. In most conflicts, the causes of mortality are indirect and noncombat related. For example, in conflict-affected Darfur, Sudan, close to 90 % of excess civilian deaths between 2003 and 2008 were due to nonviolent causes (Degomme and Guha-Sapir 2010). Conflict limits access to livelihoods, clean water, and healthy food, causes displacement and overcrowding, and disrupts health services. As a result, death rates increase, deaths that are not directly conflict related (Coghlan et al. 2006).

Not only is conflict itself a social determinant of health, social determinants of health *within* conflict-affected populations will influence the magnitude, prevalence, and distribution of substance-related harm within those populations. Aspects of material wealth, such as access to health care or differential policing patterns, make the poor more likely experience harm from substance use than the rich may experience from the same pattern of use. Health problems are compounded by limited access to good nutrition and social resources, which is frequently the case with displaced populations. Income inequality will contribute to differential development of substance-related problems – on the one hand access to cash can increase access to substances, and on the other hand limited access to services and resources will increase the likelihood of harm from substance use.

It follows, therefore, that effective intervention for substance-related harm in populations displaced by conflict requires action on the social determinants of harm. Drawing from the HIV literature, actions aimed at addressing these social determinants are increasingly termed structural interventions. Structural interventions do not aim to change individual behaviors per se; instead they aim to change the distribution of risk, health, and illness in the population. Structural interventions can be single or combination processes, policies, or programs and may have an important public health impact on multiple endpoints (not limited to substance-related harm). Growing evidence suggests that individually directed interventions have only modest impacts on risk behavior in the absence of population and policy interventions to support their effective introduction. Individual interventions target individuals (and their families) already at risk or experiencing harm; structural interventions include whole populations and have greater population impact. Figure 131.2 demonstrates this concept.

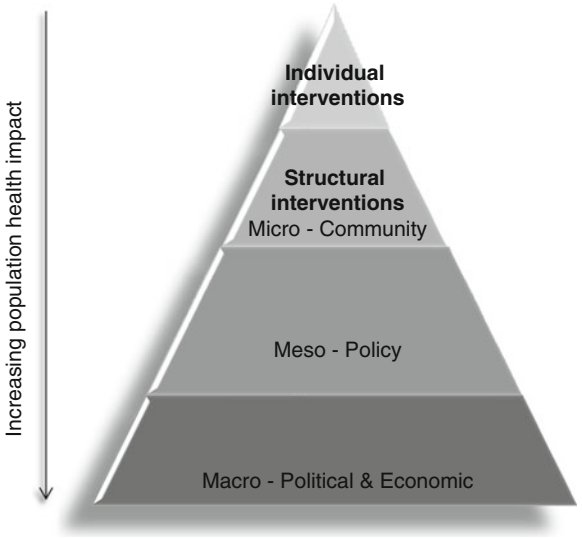

Fig. 131.2 Population intervention framework for reducing substance-related harm (Source: informed by Friedan 2010)

Experience of interventions to reduce substance-related harm among populations displaced by conflict is limited. This schema can provide a theoretical basis for identifying and organizing interventions and for evaluating their effectiveness. While changing the conditions of conflict may be beyond health professionals, the model may be useful to develop interventions within populations displaced by conflict.

Examples of individual-level interventions include biomedical interventions such as thiamine provision for heavy alcohol users and treatment of withdrawal and dependence syndromes. Other interventions include ensuring ready access to early intervention for substance-related health consequences such as hypertension, tuberculosis, sexually transmitted infections, and injuries. There is some experience in the implementation of behavioral interventions, such as screening and brief intervention aiming to decrease volume and frequency of drinking (Ezard et al. 2010). Substance use may also be incorporated into mental health programs to detect and treat depression-like illness and other locally identified mental health problems. Social interventions, such as women's safe houses, have already been introduced in some settings. Advocacy for inclusion of displaced populations into host population services may be relevant.

Individual-level interventions with evidence of effectiveness from non-displaced settings may be adapted for conflict settings. Yet it remains unclear whether these contexts are so vastly different in salient ways as to limit effectiveness. The question of how much evidence of effectiveness is necessary comes into relief. The gold standard of evidence-based interventions may not be realistic in settings of high population mobility, competing health and other priorities, resource constraints, and with complex ethical dimensions. At a minimum, interventions should be theory based and show positive outcomes on monitoring or evaluation.

Structural interventions can be divided into micro-, meso-, and macro-levels. Microlevel examples include community-based interventions to mobilize and empower marginalized and affected populations. Experience of engaging community support as therapeutic intervention for substance use problems has been described in post-conflict settings such as Kosovo (Agani et al. 2010). Effective community mobilization strategies have also been developed to address stigma around problem substance use to promote demand for services.

Community strategies like those described above are aimed at supporting individual behavior change. Others may be indicated for changing prevailing norms and attitudes, such as towards excessive drinking or violence (Jewkes et al. 2002). Efforts to modify drinking culture have met with mixed success elsewhere and need to be further investigated in displaced populations.

Experience is growing with community-based alternative income strategies for illegal drug production and for artisanal alcohol (with mixed success). The aims of these initiatives need to be clearly defined. One study from displaced camps in northern Uganda showed no relationship between women's alcohol brewing and their husband's alcohol use, or women's alcohol brewing and experience of intimate partner violence, despite a relationship between women's experience of

intimate partner violence and their husband's alcohol use (Annan and Brier 2010). In this context, then, the aim of micro-finance initiatives is not to directly decrease alcohol-related intimate partner violence. Instead, the aim is to indirectly decrease intimate partner violence through gender-based empowerment and improved livelihoods by building skills and increasing income. Indeed, there is some evidence from South Africa for micro-finance initiatives decreasing both HIV transmission and intimate partner violence (Pronyk et al. 2006).

Meso-structural interventions targeting the policy environment include limiting hours of sale, restricting age of purchase, controlling marketing, increasing taxation, and imposing minimum pricing strategies (Casswell and Thamarangsi 2009). However, these strategies apply to licit commercial markets with strong regulatory and enforcement capacity and may have limited application in conflict-affected settings. Interventions to improve the quality of artisanal alcohol such as brewer education and micro-financial incentives may be trialled in settings where the commercialization of homebrew is prominent (Kanteres et al. 2009).

Other policy interventions include equity-based initiatives by service providers. These efforts include ensuring good gender policy among interventionists, human rights-based programming, and inclusive participatory approaches to service delivery and management. Gender equity policy may address early childhood development, access to education, and high-quality childcare. A health equity approach incorporates collective and community needs, not only those of individuals. The focus is not on identifying and targeting marginalized groups so much as developing systems and processes that are socially inclusive. Socially inclusive processes of service delivery should incorporate the marginalized and avoid reinforcing existing inequalities (rather than focusing on identifying and exclusively targeting the most vulnerable).

Macrostructural changes to the political and economic context may have a profound influence on substance-related harm; acting at this level may be challenging for people working in the health sector. Actions can include drug law and economic reforms. Cross-sectoral alliances with environmental, human rights, and governance-focused groups may be directions for action, such as advocacy for refugee and migrant groups and engagement with processes governing global migration.

Structural interventions, characterized by multiple components and multiple endpoints, are complex to evaluate. Evaluation is even more challenging when attempts are made to include difficult-to-measure endpoints such as "hopefulness." Nevertheless, the effectiveness of these interventions must be assessed and the results disseminated. These types of interventions may not readily lend themselves to existing methods for assessing effectiveness and demand new approaches. Gupta and colleagues suggest a "realistic evaluation" approach, which relies heavily on qualitative process assessment as well as evidence from elements along the hypothesized causal chain (Gupta et al. 2008). Common endpoints with other interventions, such as violence prevention, should be recognized, as should consequences for substance use of other interventions.

131.6 Conclusion

Substance use among populations displaced by conflict is an important area of public health endeavor. Effectively intervening to minimize harm related to substance use requires an understanding of the social context in which substance use occurs. This chapter has described how conflict can shape transitions in substance use and development of substance-related harm. By highlighting the social determinants of substance-related harm in these populations, interventions can be identified that address these determinants. Effectively minimizing harm from substance use among conflict-displaced populations requires a combination of individual, micro-, meso-, and macrostructural interventions.

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Disaster Exposure, Substance Use, and Related Outcomes Among Youth: Linkage and Treatment Implications

132

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Contents

Abstract

This chapter examines studies involving adolescents and young adults exposed to disasters and reviews evidence for a range of disaster effects with an emphasis on substance use. Implications for treatment are also addressed. Available

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evidence suggests that while many young people experience distress in the immediate aftermath of a disaster, a majority recover within a year and maintain a pattern of adequate functioning. A minority reveal clinically meaningful levels of PTSD, substance abuse, or post-disaster increases in substance use. Objective and subjective disaster exposure has been linked with psychological symptoms and increases in substance use. Further, substance use among disaster survivors is associated with impaired behavior and poor performance in school. Parents, school personnel, and health professionals are encouraged to be vigilant and monitor disaster survivors for signs of enduring distress, substance abuse, and impaired functioning. Possible pathways to development of comorbid PTSD and substance abuse are reviewed and promising integrated treatment programs are identified. Multisystemic models of intervention are likely well suited to address the various dimensions of disaster impact and recovery among youth most adversely affected. However, the need for controlled clinical trials involving these and other promising interventions for disaster-impacted youth is apparent.

132.1 Introduction

There is evidence that individuals exposed to major disasters experience a range of psychological and stress-related physical problems including PTSD, other anxiety reactions, depression, grief, suicidal ideation, and substance abuse (Shore et al. 1986; Goenjian et al. 1995; Staab et al. 1996; Vernberg et al. 1996; North et al. 1999; Bolton et al. 2000; Hoven et al. 2003; Rehner et al. 2000; Nandi et al. 2005; Roussos et al. 2005; Chen and Wu 2006; Kar and Bastia 2006; Vehid et al. 2006; Mortensen et al. 2009; van der Velden and Kleber 2009; Bonanno et al. 2010). It is easy to assume that most individuals who experience disaster will require treatment. However, careful evaluation of the nature and extent of disaster-related impact is necessary to develop and appropriately allocate treatment resources. A disaster's impact depends not only on degree of exposure to disaster-related events but also on a variety of individual, family, and community risk and protective factors. In fact, the majority of exposed individuals demonstrate resilience after experiencing potentially traumatic events, reporting only temporary distress while sustaining a pattern of healthy functioning. Studies of both adults and children typically reveal that fewer than 30 % demonstrate persistent symptom elevation (Bonanno 2005).

Multiple risk and protective factors have been identified as potentially significant in distinguishing individuals likely to be adversely impacted from those likely to adapt favorably. Among these factors are demographic characteristics including age, gender, ethnic minority status, and level of education; degree of exposure to potentially traumatic events; the number and nature of secondary stressors experienced in the disaster aftermath; social and material resources as well as loss of such resources post-disaster; personal and family history of psychiatric disturbance; and person-focused variables including neuroticism, hardiness, and self-enhancement (Green et al. 1991; Norris 1992; Garrison et al. 1993; Thompson et al. 1993; Bokszczanin 2007; Bonanno et al. 2010). Results of these studies are not consistent.

However, youth and old age, relatively high subjective or objective impact of disaster, lack of a support system, and pre-disaster psychological difficulties are all associated with post-disaster problems (e.g., PTS, substance use). A substantial amount of research on psychosocial consequences of disaster exposure has focused on adults, and considerable emphasis has been placed on PTSD as an outcome. Much less attention has been devoted to effects on youth and other outcomes such as alcohol and other drug use.

This chapter will examine studies involving adolescents and young adults exposed to disasters and will review evidence for a range of disaster effects with an emphasis on substance use. Implications for treatment will also be addressed. At the outset, it is important to note the challenges of conducting careful research on effects of disasters. Because disasters are infrequent and unpredictable, pre-disaster measurements of potentially critical personal and social contextual predictors of disaster outcomes are typically unavailable. Recall bias and inaccurate memory of disaster-linked past events and behaviors may limit the value of post-disaster assessments. Collecting data in the immediate wake of a disaster is challenging limited availability of individuals most severely impacted may contribute to biased samples. Institutional review boards are often burdened with achieving a delicate balance between expediting data collection to support evidence-based response and guarding against the approval of multiple redundant studies and protecting the human subjects who have already experienced excessive stress (Fleischman et al. 2006). Furthermore, disasters vary widely in nature and severity and involve different types of damage and rates of mortality. Findings based on data from communities that experienced severe earthquakes may not apply to those that experienced floods or fires. Similarly, impact of disaster on use of substances ranging from alcohol and cigarettes to harder, illegal drugs such as cocaine may be contingent on pre-disaster substance use, access to substances post-disasters, or other factors which may lead to inconsistent findings in disaster-related studies. Yet another challenge to the generalizability of study findings involving disasters is the fact that these events often occur in communities that have distinct socioeconomic characteristics that influence availability of resources necessary for recovery. Members of a wealthy community in the suburb of a major metropolitan area may experience and respond to disaster differently than members of a poor rural community. With these challenges in mind, we review studies in which disaster exposure among youth is examined in association with substance use and related outcomes.

132.2 Disasters and Youth: Substance Use and Related Outcomes

132.2.1 Linking Disaster Exposure, Substance Use, and Associated Problems

After conducting several electronic literature searches up through June 1, 2013 (PubMed, OVID, Medinfo, PsycINFO, and first 100 pages of Google Scholar), we

were only able to locate six well-designed studies that examined relationships between disaster exposure and substance use among adolescents and young adults.

Chemtob et al. (2009) examined associations between exposure to the World Trade Center (WTC) attacks on September 11, 2001, and levels of substance use, psychiatric symptoms, functional impairment, and mental health service utilization 18 months post-9/11 among a convenience sample of 1,040 middle and high school students whose schools varied in proximity to the WTC. Subjects were from diverse ethnic backgrounds (33 % Asian, 13 % African-American, 19 % Hispanic, 17 % Caucasian, and 18 % multiracial and others), and 55 % were female. Objective and subjective indices of disaster exposure included (a) death of known individuals, (b) proximity of school to attack site, (c) worry about personal safety, (d) worry about safety of others, and (e) parental impairment. Criterion and control measures included self-reports of increased substance use, PTSD symptoms, depression, functional impairment reflected in difficulty getting along with friends and family, schoolwork difficulties, poor grades, behavioral problems at school, difficulty with teachers, pre-9/11 and post-9/11 mental health service utilization, and desire for mental health assistance with 9/11 reactions.

Approximately 10 % of participants reported increased substance use post-9/11 with smaller proportions revealing impairment in friendships, family, and school performance. PTSD diagnosis, while infrequent, was strongly associated with impairment in these areas. Logistic regression was used to evaluate associations between risk factors and both disorder symptoms and functional impairment. Indices of trauma exposure including worry about others' safety, loss, parental impairment, and proximity to the WTC were linked with likelihood of reporting increases in substance use. Participants with one exposure risk factor were more than 5 times more likely to report an increase in substance use than those with no exposure risk factors, those with two were more than 8 times more likely, and those with three or more risk factors were nearly 19 times more likely. Increased substance use was linked with functional impairment in behavior at school, in schoolwork, and in grades. Adolescents who had revealed increased substance use were more likely than those who had not to demonstrate functional impairment in behavior at school (6.7 % compared to 3 %), in schoolwork (18.1 % compared to 7.8 %), and in grades (38.2 % compared to 0 %). All students whose grades declined reported increased substance use. Further, those who reported increased substance abuse were nearly twice as likely to want mental health services 1½ years after the attack but were not more likely to receive them. Finally, those reporting increased substance use, PTSD, or depression were not more likely to have received mental health services before 9/11 than those without these characteristics. Compared to those who had not increased substance use, adolescents who had increased substance use were more than twice as likely to want mental health services 18 months after 9/11, but they had about the same likelihood of receiving such services (11.2 % vs. 13.8 %). Youth who had increased substance use without experiencing PTSD or depression were even less likely to receive services.

Rohrbach et al. (2009) explored relationships among exposure to Hurricane Rita, post-traumatic stress (PTS) symptoms, and changes in adolescent substance use

from 13 months pre-disaster to 7 and 19 months post-disaster. Subjects were 280 high school students recruited from ten schools in southwestern Louisiana that participated in a national dissemination trial of substance use prevention and lived in areas where storm effects caused widespread electrical outages, human causalities, and destruction to property. Nearly 68 % of participants were female and a similar proportion was white. Surveys were administered 13 months prior to the hurricane and 7 and 19 months after the hurricane. At each assessment, use of cigarettes, alcohol, and marijuana over the past 30 days was evaluated. PTS symptoms were assessed at 7 months post-hurricane. Researchers used measures that distinguished between objective hurricane exposure (e.g., hurt in hurricane, property damaged, had to move) and subjective exposure (e.g., experienced fear, thought life was in danger). Post-hurricane negative life events that might have occurred to the individual (e.g., relationship breakup) or to the individual's family (e.g., problems with money) were assessed at 7 months post-hurricane.

Although the majority of participants (>75 %) reported nonuse of cigarettes and marijuana both at baseline and follow-up, a minority (8–15 %) reported change from nonuse to use at follow-up. Forty-seven percent reported nonuse of alcohol at baseline and follow-up; however, about a quarter changed from nonuse at baseline to use at follow-up. Objective hurricane exposure assessed at 7 months post-hurricane was associated with increased cigarette use from baseline to 7 and 19 months and with increased marijuana use from baseline to 19 months. Post-hurricane negative life event exposure was linked with increases in all three substances at 7 months and with increased cigarette and marijuana use at 19 months. Although PTS severity was linked with alcohol and marijuana use at 7 months and with marijuana use at 19 months, most participants reported few such symptoms and these relationships were not significant when other predictors (e.g., storm exposure and negative events) were controlled.

Cepeda et al. (2010) investigated demographic variables, criminal history, lifetime trauma exposure, and hurricane impact variables in relation to changes in substance use among economically disadvantaged drug users who were evacuated from New Orleans due to Hurricane Katrina in August 2005. Data were gathered from July 2006 to January 2007 using semi-structured interviews with 200 evacuees participating in an ongoing drug abuse study in Houston. Participants were 18–65 years old with a mean age of 32. Ninety-eight percent of the sample was African-American and 60 % was male. Ninety percent of participants reported that their home was demolished or uninhabitable and 63 % reported they left New Orleans after the hurricane. Prior to the hurricane, tobacco, alcohol, and marijuana were each used by about 70 % of the sample. Tranquilizers, barbiturates, or sedatives were used by 31 % of the sample, ecstasy and crack were each used by 25 %, and cocaine was used by 19 %.

Of particular interest in this study is a comparison of changes in substance use among younger evacuees (18–28) and older evacuees (29–58). In addition to age, demographic variables included gender, education, marital and parental status, and income before the hurricane. Hurricane impact variables included time of evacuation (before or after the hurricane), a disaster-related exposure score, and a resource

loss score. Profiles of change in substance use were based on self-reported frequency of use during the 30 days before the hurricane and the 30 days before the interview. Substance use change profiles reflected increased or decreased use of alcohol and/or tobacco (AT) and increased or decreased use of illicit drugs (ID; barbiturates, cocaine, crack, ecstasy, marijuana, sedatives, and tranquilizers). Overall, increases in tobacco use, alcohol, and marijuana were reported by about 30 % of the sample. Twenty-three percent increased use of ecstasy, 14 % increased use of tranquilizers, barbiturates, or sedatives, 12 % increased use of crack, and 8 % increased use of cocaine. Larger proportions reported decreased use of all substances except for tobacco. Seventy-two percent of the sample decreased cocaine use; 65 % decreased tranquilizer, barbiturate, or sedative use; 57 % decreased crack use; 36 % decreased ecstasy use; 35 % decreased alcohol use; 27 % decreased marijuana use; and 16 % decreased tobacco use.

Chi-square tests were used to identify significant associations between predictor variables and increases and decreases in AT and ID use. Factors with significant associations ($p < 0.10$) were included in follow-up multivariate logistic regression analyses to identify the same changes in profiles of use identified earlier. Multivariate analyses revealed that younger evacuees were more likely than older evacuees to increase use of alcohol and tobacco (52 % vs. 36 %) and less likely to decrease use of both alcohol and tobacco (29 % vs. 43 %) and illicit drugs (40 % vs. 55 %) in the 11–17 months following the disaster. Also of interest, women were more likely than men to increase use of AT (54 % vs. 38 %). Evacuees with more education were more likely to increase use of AT (52 % vs. 39 %), as were evacuees who left New Orleans before Katrina compared to those who left after the hurricane (54 % vs. 38 %). Individuals who reported high resource loss were more likely than those who reported moderate resource loss to increase use of ID (56 % vs. 40 %). Perhaps surprisingly, evacuees with a criminal history were more likely than those with no such history to decrease use of ID (55 % vs. 41 %). Individuals with a moderate total score on disaster-related exposure were more likely than those with a high score to decrease use of AT (57 % vs. 31 %) but less likely to decrease use of ID (32 % vs. 52 %).

Overstreet et al. (2010) examined relationships between initial hurricane impact, "secondary stressors" thought to be important in post-disaster environments, and crime exposure in relation to PTSD symptoms among high school students exposed to Hurricane Katrina. Both direct and moderating influences of substance use were also evaluated. Of the 261 participants included in the analysis, 54 % were considered to be economically disadvantaged, 55 % were female, 41 % identified as black, and 50 % identified as white.

Surveys were distributed by homeroom teachers and completed by 76 % of students. Four items from a 12-item measure of various Katrina-related disruptions were used to create two predictor variables: initial impact and crime exposure. These items were as follows: "How many schools have you attended since August 29, 2005?," "How many times have you moved since August 29, 2005?," "Did one of your parents lose his or her job because of the disaster?," and "Have you or members of your family been the victim of crime?" Level of exposure to secondary

stressors was assessed using eight items reflecting the current status of hurricane-related disruptions (e.g., "Has it been hard to see your friends since the evacuation?"). Three of these were drawn from an existing measure of hurricane-related disruptions (e.g., ongoing damage to one's home, parental job loss, difficulty seeing friends). PTSD symptoms were assessed using selected items from the adolescent version of the Los Angeles Symptom Checklist (LASC). Substance use was assessed using two items from the LASC, dichotomized to reflect nonuse or some use. Ninety-two percent of participants experienced at least one secondary stressor, with nearly half experiencing three or more. The most common secondary stressors involved disruptions in contact with friends. Twenty-six percent of participants scored in the clinically elevated range of PTSD symptoms. This proportion is similar to those found in other post-disaster studies. Females reported significantly more PTSD symptoms than males but similar levels of secondary stressors. Fourteen percent of participants reported substance use, consistent with previous post-disaster studies. There were no gender differences in substance use.

Analysis of bivariate relationships revealed significant associations between gender, secondary stressors, as well as problem substance use and both an overall index of PTSD symptoms and specific measures of reexperiencing, avoidance/numbing, and hyperarousal. Secondary stressor exposure was significantly associated with problem substance use; however, initial hurricane impact was not. Hierarchical regression analysis was used to determine if gender, initial hurricane impact, crime exposure, secondary stressor levels, problem substance use, and a variable reflecting the interaction of secondary stressors and substance use contributed to prediction of overall PTSD symptoms. Gender and crime exposure entered in the first block contributed significantly to prediction of PTSD symptoms. Females and those with higher levels of crime exposure experienced more symptoms. Initial hurricane impact did not predict PTSD symptom level. Secondary stressors and problem substance use, entered in the second block, contributed significantly, with problem substance use contributing most to prediction. The secondary stressor moderating influence of substance use was examined in the final block but it did not contribute significantly to prediction of PTSD symptoms.

Rowe et al. (2010) studied hurricane impact variables, individual, and family factors in relation to substance involvement and post-traumatic stress symptoms in a group of adolescents exposed to Hurricane Katrina. Eighty adolescents and their parents were interviewed at substance abuse treatment intake between 16 and 46 months after the hurricane. The majority of participants were male (87 %) and between 13 and 17 years of age. Sixty-two percent were white, 31 % African-American, and 4 % Hispanic. Pre-disaster predictors included demographics, adolescent and parent substance abuse, and pre-disaster trauma exposure. Hurricane impact variables included initial loss/disruption and perceived life threat. Post-disaster variables included family psychopathology, family cohesion, parental monitoring, and adolescent delinquency. Participant scores on the adolescent self-report and parent reports of adolescent symptoms reflected mild PTS symptom severity on average. Substance use scores were also within a mild range of severity on average. Hierarchical regression analysis revealed that greater hurricane-related

loss/disruption, lower family cohesion, and greater adolescent delinquency were linked with greater adolescent-reported symptoms of post-traumatic stress. Parental psychopathology, lower family cohesion, and less parental monitoring were associated with parental reports of adolescent PTS. Adolescent substance use involvement was associated with lower parental monitoring, higher adolescent delinquency, and higher family income. Hurricane-related variables were not significantly related to adolescent substance involvement.

Parslow and Jorm (2006) explored the experience of traumatic events, immediate disaster-related emotional response, and fire-related PTSD symptoms of reexperiencing and hyperarousal in association with changes in tobacco consumption in a sample of 2063 young adults living in a region of Australia impacted by a major bushfire in 2003. Participants were between 20 and 24 years of age at the time of the initial evaluation, which took place several years prior to the disaster (1999–2000). The follow-up evaluation was conducted 4 years later (2003–2004), a few months after the fire occurred. A majority (62 %) lived or worked in an area that was put on alert and about half reported that friends or relatives had experienced fire-related damage. Smaller proportions reported forced evacuation from home or own workplace (11 %), possessions damaged (3.9 %), personal injury (1.9 %), or death or injury of a personal friend or relative (4.7 %). Nearly 14 % reported personal involvement in fighting bushfires threatening home or neighborhood, and nearly one fifth reported other work involving bushfires and their effects. Five percent of the sample fit criteria for PTSD with the majority reporting no PTSD symptoms in the week prior to evaluation. Over the 4 years of the study, 13 % of participants increased tobacco use. Those reporting more traumatic events experienced during the disaster were slightly more likely to report increased consumption of tobacco (OR: 1.12, 95 % CI: 1.03–1.21). This relationship applied only to those who reported some tobacco use at the initial assessment. A higher proportion with PTSD hyperarousal symptoms reported increased tobacco use (31.1 % vs. 24.9 %; $p = 0.018$). This relationship was no longer significant after controlling the number of traumatic events experienced.

132.2.2 Treatment Implications and Recommendations: When and With Whom to Intervene

Evidence from the studies reviewed suggests that a minority of adolescents and young adults exposed to disasters reveal clinically meaningful levels of PTSD, substance use, or post-disaster increases in levels of substance use. However, consistent with the adult literature, there is evidence that higher levels of objective and subjective disaster exposure are linked with greater psychological symptoms and increases in substance use (Green et al. 1994; Parslow and Jorm 2006; Chemtob et al. 2009; Rohrbach et al. 2009; Cepeda et al. 2010; Rowe et al. 2010). Further, increased substance use has been linked with functional impairment in behavior and

performance in school (Chemtob et al. 2009). Although most young people are expected to experience distress in the immediate aftermath of a disaster, the majority recover within a year and maintain a pattern of adequate functioning (La Greca et al. 1996; Chen and Wu 2006; Bonanno et al. 2010). That said, school personnel and health professionals should be vigilant and monitor disaster survivors for signs of enduring distress, substance abuse, and impaired school functioning (Chemtob et al. 2009; Rohrbach et al. 2009). It has been argued that school-based monitoring and treatment resources should be made available to facilitate assessment and intervention when needed (Chemtob et al. 2002, 2009; Joshi and O'Donnell 2003; Taylor and Chemtob 2004).

Vernberg (2002) distinguished post-disaster interventions on the basis of phase of recovery. While a number of interventions have been designed for implementation in the immediate aftermath of disasters or terrorism, there is little evidence that psychological interventions in this time frame effectively reduce immediate distress or improve longer-term outcomes (La Greca 2008; La Greca and Silverman 2009). La Greca and Silverman (2009) suggest best practices include having adults provide comfort and reassurance; encourage expression of concerns, fears, and apprehensions; and assist youth in returning to normal activities and routines. During this phase, adult caretakers might be assisted in identifying acute stress reactions that require evaluation and treatment.

In the next phase, short-term recovery (from the first few weeks to the first year post-disaster), La Greca and Silverman (2009) recommend a focus on building coping skills for dealing with emotional reactions and predictable stressors in the disaster aftermath, reestablishing supportive social relationships, and continuing to encourage a return to normal roles and routines. A number of psychoeducational resources have been developed to accomplish these objectives (La Greca et al. 1994, 2001; Prinstein et al. 1996; Gurwitch et al. 2005). Although promising, little is known about the effectiveness of these informational approaches. As in the initial phase, there is a need to identify youth with moderate to severe symptoms who may need careful evaluation and treatment.

Although most youth recover during the first year after exposure to traumatic events, a significant minority experience chronic stress reactions (La Greca et al. 1996, 2002). Current interventions typically target persistent or chronic youth PTSD reactions, and cognitive behavioral therapy (CBT) is the treatment approach about which most is known (Brady and Back 2012). CBT is thought to promote habituation by targeting stimulus–response associations and correcting distorted cognitions. Prolonged exposure approaches involve psychoeducation, breathing retraining, imaginal exposure to trauma memory, and in vivo exposure to trauma reminders (Rachman 1980; Deblinger et al. 2001; Vernberg 2002; Cohen et al. 2004, 2005; La Greca and Silverman 2009). These interventions have been effective in treatment of abuse victims and may reduce PTSD symptoms in youth (Deblinger et al. 2001; La Greca et al. 2002; Cohen et al. 2004, 2005). It should be noted that some research has shown that unnecessary reexposure may trigger substance abuse and other problems (Brady et al. 2013).

132.2.3 Understanding and Addressing Comorbid Substance Abuse and PTSD

There are likely multiple pathways to development of comorbid PTSD and substance abuse among youth exposed to disasters, but few studies have examined this issue. It is often assumed that PTSD emerges initially and substance use and abuse follow reflecting efforts to cope with post-traumatic symptoms. The link between traumatic event exposure and substance abuse is argued to be mediated by PTSD and/or other psychiatric symptoms (Souza and Spates 2008). A number of the studies reviewed earlier identified a relationship between disaster event exposure and both PTSD symptoms and substance abuse (Parslow and Jorm 2006; Chemtob et al. 2009; Rohrbach et al. 2009). Although none of these studies included formal mediation analysis, conditions for mediation did not appear to be met. In Rohrbach et al. (2009) and Parslow and Jorm (2006), associations between PTS symptom severity and substance abuse increases were no longer significant when indices of disaster exposure were controlled. Rowe et al. (2010) found that among adolescents exposed to Hurricane Katrina prior to entry into substance abuse treatment, degree of loss and disruption associated with the hurricane exposure, while linked with PTSD symptom elevation, was not associated with level of substance involvement. This study employed a cross-sectional design and could not illuminate potential causal linkages among event exposure, PTS, and substance use.

Other PTSD vulnerability factors (e.g., minority ethnic status, female gender, lack of education, and younger age) have been argued to moderate the relationship between exposure and substance use initiation or increase in use. Unfortunately, few studies involving youth have examined the contribution of these potentially important factors. Cepeda et al. (2010) found that among economically disadvantaged drug users, younger evacuees from New Orleans during Hurricane Katrina were more likely to increase use of alcohol and tobacco and less likely to decrease use of alcohol, tobacco, and illicit drugs than older evacuees. They also found elevated risk among females and among those with more education.

While little research has addressed pathways leading to PTSD–SA comorbidity among youth exposed to disasters, further exploration in this area may be important in identifying streams of influence necessary to address when developing treatments (Souza and Spates 2008). In the adult literature, it has frequently been assumed that PTSD is a major risk factor for development of substance use. PTSD-related intrusive thoughts, negative emotions, and hyperarousal symptoms have been linked with increased craving for substances following presentation of trauma-related stimuli (Marlatt and Gordon 1985; Sharkansky et al. 1999; Souza and Spates 2008). There is some evidence that substance abusers are more vulnerable to developing PTSD after trauma exposure and the effects of some substances (i.e., cocaine) may exacerbate PTSD symptoms (Sharkansky et al. 1999). Further, negative impact of high SA risk situations may complicate the substance user's ability to cope with the symptoms of PTSD (Souza and Spates 2008). Those with co-occurring PTSD and substance abuse demonstrate higher levels of interpersonal

conflict, less self-efficacy, and more limited ability to cope with psychological distress compared with those showing only substance abuse (Ouimette et al. 1999; Sharkansky et al. 1999). Indeed, the co-occurrence of substance abuse and PTSD may be linked with the severity of symptom presentation of both conditions and may complicate treatment of each. Although clinical folklore favors initial treatment of substance problems followed by attention to PTSD issues, increasing emphasis has been placed on integrated treatment models that address PTSD issues relatively early in treatment (Souza and Spates 2008). There are likely multiple pathways to development of comorbid PTSD–SA among youth exposed to disasters, but few studies have examined this issue. A randomized, controlled study comparing outcomes of adolescent females with comorbid PTSD and substance abuse treated with *Seeking Safety* to those who underwent "treatment as usual" found that the group treated with *Seeking Safety* had significantly better outcomes in several areas, including some trauma-related symptoms and substance use (Najavits et al. 2006). This approach has not yet been studied in disaster-involved youth.

132.2.4 Broadening the Perspective: Multisystemic Approaches

Bonanno et al. (2010) emphasize that disasters have an enduring negative psychological impact on a minority of individuals exposed, that exposure outcomes vary considerably and depend on a combination of risk and resilience factors, and that effects on families, neighborhoods, and communities are important to consider because disasters can damage these critical social units. Youth are at risk for a range of negative outcomes under conditions of individual, family, and community disorganization (Hawkins et al. 1992; Newcomb and Felix-Ortiz 1992; Rowe and Liddle 2008). The loss of or disruption to crucial community structures may have particular impact on youth already at elevated risk (Rowe and Liddle 2008). Typical service structures available for working with young disaster victims, their families, and communities are often not well equipped to address complex co-occurring psychiatric conditions (e.g., PTSD–SA), as well as disruption to already high-risk families, neighborhoods, and communities (Rowe and Liddle 2008). Multisystemic models of intervention seem particularly well suited to deal with the multiple dimensions of disaster impact and recovery among those severely affected. However, little research has addressed the efficacy of such models in disaster-impacted communities.

Hawkins et al. (1992) have developed both assessment and intervention programs that enable evaluation of the particular needs of individuals, schools, and communities and argue for tailoring intervention efforts on the basis of careful needs assessment. Another promising model, Multidimensional Family Therapy (MDFT; Liddle 2002), is being evaluated in a randomized trial with clinically referred substance-abusing teens in a New Orleans area community impacted by Hurricane Katrina (Rowe and Liddle 2008). Bonanno et al. (2010) emphasize that it is important to improve and mobilize essential community resources following a massive disaster (Norris et al. 2002; Somasundaram et al. 2003;

Hobfoll et al. 2007). However, when large-scale resources are suddenly imported, care must also be taken not to harm to the post-disaster community's fragile cohesiveness and sense of efficacy (Kaniasty 2012).

132.3 Conclusion

The studies reviewed may suggest at least three programmatic directions specifically relevant to youth. First, some type of family treatment may be important to increasing monitoring of youth and family cohesion and to dampen potential impact of a disaster on PTS and substance use. Knowing youths' whereabouts and providing grounding in a meaningful home lifestyle are imperative when the environment has become suddenly and dramatically disorganized. The treatments suggested above (e.g., MDFT) may assist in that regard. One may speculate that provision of family-based substance abuse prevention programming such as the Strengthening Families Program (SFP) or Family Matters (FM) might also provide a protective impact prior to the experience of disaster (Sussman 2013). In fact, use of prevention programming may benefit outcomes by lessening the need for post-disaster treatment that may elicit negative side effects (e.g., sensitization to the disaster, demoralization; Wagner et al. 2009).

Second, evaluating mental health and substance abuse treatment needs of, and providing needed treatment to, high-risk youth as soon as possible post-disaster is indicated. Lack of personal and social resources (e.g., adequate coping skills and social support) has been a reality for survivors of many disasters and impedes recovery from PTS and drug misuse (Wagner et al. 2009). The need for controlled clinical trials of treatments for youth presenting with SA and/or PTSD is obvious. The Multidimensional Family Therapy study of Hurricane Katrina-exposed, substance-abusing youth is an important effort in this area (Rowe and Liddle 2008).

Finally, providing instrumental environmental resources (e.g., insurance, medical care, employment, and housing) and capacity to create an organized, restructured, restorative environment as soon as possible (to reduce post-disaster crime or other secondary trauma exposure) is needed to embed youth within a safe community context in which family support could be maximal and individual resilience might be reinforced (Wagner et al. 2009).

The conclusions and recommendations found in the chapter are only suggestive because of (a) the paucity of work in this arena, (b) the existence of retrospective report confounds in most studies (all but the Rohrbach et al. study), and (c) numerous variations across these few available studies (e.g., types of disaster, age of youth, SES of context). However, we believe in erring on the side of caution and carefully evaluating and addressing the needs of those most vulnerable and most seriously impacted. Most studies on youth have been conducted in highly developed locations. In less-developed locales (e.g., post-disaster circumstances in Haiti), providing needed assistance may require more extreme measures just to stave off starvation. Clearly, more research is needed to assess both the amount and nature of assistance that can be most beneficial to youth post-disaster.

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Section XI

Children, Adolescents and Young Adults

Ilana B. Crome and Robert Milin

Children, Adolescents and Young Adults: An Introduction

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Ilana B. Crome and Robert Milin

Abstract

One of the major challenges that young people face is the risk of initiating substance use, which is especially high at this age. It is a vital area of study because if we can effectively intervene early, we will prevent chronicity as well as the potential development of other mental disorders and even premature death, with its impact on families and community. It is vital because an understanding of the mechanism of development in young people may provide pointers to understanding the nature of addiction. Promising interventions for adolescents who misuse substances have been identified and we should build on findings to date to further enhance methods to improve treatment outcome, accessibility, implementation, and relapse prevention through the integration of research findings into treatment.

Little seems to engender so much disquiet as young people who use drugs. This is for many obvious, and sometimes not so obvious, reasons. There is fear, concern, and worry. This can be justified, since one of the major challenges that young people face is the risk of initiating substance use, which is especially high at this age. This may result in a plethora of unwanted acute and chronic social,

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psychological, and physical consequences and may occasionally be life-threatening. The risk of self-harm and suicide is of concern to clinicians for every patient they assess.

Intervention improves outcomes; thus, it is right that substance use in adolescence is an area of significant individual and public health concern. It is also likely that the earlier the intervention, the more chance there may be of a successful outcome.

So, while there is every reason for parents and the communities in which we live to feel apprehensive, we have attempted to focus on a few key areas in this domain, where promising advances over the last decade have elucidated our understanding and treatment of young people with substance use problems.

We have been fortunate that our colleagues from across the globe have agreed to contribute to this vital topic. It is vital because the majority of people who experience lifelong substance use problems have started in their teenage years. In some, their mothers and fathers will have suffered too. Therefore, this young cohort gives us clues about the degree to which substance problems may be inherited genetically and the product of environment.

It is a vital area of study because if we can effectively intervene early, we will prevent chronicity as well as the potential development of other mental disorders and even premature death, with its impact on families and community. It is vital because an understanding of the mechanism of development in young people may provide pointers to understanding the nature of addiction.

Thus, we have chosen topics that are important and controversial, and authors have critically analyzed the material which they have presented:

The overview chapter by Milin and Walker which focuses on enhancing comprehension of adolescent substance use disorders (SUD) in addressing the following areas, epidemiology, vulnerability and developmental course, comorbidity, assessment, treatment, and outcomes, provides us with a valuable synopsis of the current state of knowledge on adolescent SUD.

Schlosberg and Shoval remind us that suicide is the second or third leading cause of death among adolescents in the industrialized world. They present data which substantiates that the connection between suicide and substance abuse in adolescents is very strong and poses substance use disorders as a major risk factor for emergent suicidal behaviors. They highlight the role of salient moderating factors such as comorbid psychiatric pathologies, age, gender, and sexual minorities.

Dr. Brook and colleagues have demonstrated that adolescent substance use is best understood as determined by a multitude of risk factors in different developmental contexts (i.e., individual, micro-and macro-contextual). However, it also describes how the developmental pathways to adolescent substance use can be modified by protective factors, including an attachment between parents and children, which have the ability to mitigate the impact of risk factors on adolescent substance use and abuse. Of particular importance, they draw attention as to how this knowledge can optimize preventive strategies and note the importance of cultural and developmental relevance and appropriateness in prevention.

Dr. Chang has placed a spotlight on the paradox that the treatment of ADHD in this population is often with medications with a risk of diversion and hence abuse.

He reviews clinical trials so as to understand the relative benefits versus risks because of their clinical relevance. A review of the literature in these areas leads then to an effort to translate research findings into relevant clinical practice that maximizes benefits but minimize risks.

Drs. Velez and Janssen alert us to the fact that it has been established that in utero exposure to psychoactive substances is one of the major preventable causes of disorders of fetal and infant/child growth and neurodevelopment. The effects of these neurodevelopmental alterations can appear at any time of the individual's life and can affect a variety of domains including developmental, behavioral, cognitive, and adaptive functioning. Moreover, maternal chronic substance use can compromise the maternal neural circuitries that subserve executive functioning and the regulation of stress response and consequently the ability to appropriately parent children. It is fascinating that the expression of the teratogenic effects of perinatal exposure to substances can be exacerbated by a toxic or unstable prenatal and/or postnatal environment and ameliorated by a nurturing and stable one.

Drs. Aklin and Chambers have provided an absorbing examination of the integration of translational science into adolescent addiction which has the potential to greatly improve treatment outcomes and relapse prevention. Areas of research that focus on potential behavioral and neurobehavioral targets have direct implications for treatment efficacy and build on the current treatments that have been successful. This is of great public health importance, given the clear relationship between initiating treatment, remaining in treatment, long-term abstinence, and relapse. Developmentally appropriate, targeted treatments are likely to be more efficient and potent, require less staff time, lead to less relapse, and ultimately reduce the burden on providers.

What are the striking commonalities that emerge? The first is that substance use is mainstream – it is not exceptional any longer. It has percolated through to younger age groups and can be understood through the developmental lens of adolescence and young adulthood.

A second thread is that substance misuse in young people is not just the responsibility of direct face-to-face interaction with medical professionals when a young person has an identifiable clinical "problem." It is a public health issue in that some of the precursors are socially determined and ramifications have impact on the community beyond the individual themselves.

Another common feature is that of engagement of a young person who is often vulnerable, even marginalized. There are a host of factors which may limit the degree to which a young person – and their family – might be willing to become engaged. This may depend as much on features of the intervention program as the individual and family seeking treatment. The inclusion of ongoing screening for substance use in adolescents as part of primary care may facilitate the necessary discussion of substance use and misuse.

A further notion which cuts across all contributions to this section is that of the need for coordination since teenagers who misuse substances will require involvement of multiple systems. This will include holistic and systematic and often repeated assessment. It will include coordination of health services such as primary

health care, specialist mental health, substance misuse, and general medical services. It will include coordination with other providers such as educational, criminal justice, and child welfare services. Young people with combined mental and substance use disorders exhibit greater severity of clinical symptoms, functional impairment, poorer response to treatment, and service utilization.

An additional unifying observation is that account needs to be taken of the total psychosocial environment of the adolescent at the point of assessment through to intervention and that this needs to be a continuous process due to the rapidly changing nature of adolescent substance use which can be unpredictable. Furthermore, there is agreement that effective preventive and treatment interventions must be developmentally, as well as culturally, appropriate and should be tailored to the individual's developmental stage and cultural context. Importantly, treatment itself can be preventive in terms for further deterioration.

Greater specificity in treatment choice which is explicitly tailored to the individual resonates throughout. For, although the research base has expanded enormously over the last decade, this itself leads to the conclusion that understanding is still at a relatively early stage! Broadly, psychosocial family-based interventions and developmentally appropriate CBT with MET as part of outpatient interventions have been demonstrated to provide the most consistent gains. There is accumulating evidence that supports the benefit of adolescent SUD treatment programs across different settings, including residential, short-term residential/inpatient, partial hospitalization/day treatment and outpatients, as well as some promising findings with respect to aftercare. This is encouraging. However, we are still not in a position to select which treatment modality might be more suited and effective for a particular patient. Indeed, contributors consider that involvement of the family and community is pivotal in the implementation of change.

Principally, there is a consensus for a need for larger studies with regard to the place of extended or maintenance pharmacological therapies for young people with substance use problems, especially in those with comorbid mental health problems. This represents the majority of adolescent substance misusers in residential/inpatient facilities: there are substantial implications for initial engagement, quite apart from retention in treatment, with the young person who has combined disorders. Rapid entry to treatment enhances retention.

Despite this, while effectiveness of treatment has improved, service utilization has remained relatively stable. It is also the case that, in many countries, the development of service provision has not matched need. Why is this? What are the barriers? Introduction and implementation of novel interventions can be problematic: staff are not always susceptible to change. Although the most severely afflicted young people may be treated in inpatient units, at least initially, the possibility of supporting teenagers in their communities might meet with greater success. Weighty barriers remain such as stigma, safety, transportation, family commitment, and need resolution. Mutual aid is another growing area especially if continuing care is required to sustain recovery. In keeping with this, all authors emphasize that appreciation be given to the developmental stage of the young person and their cultural background.

That the use of new technologies may support investigations is emerged as a key consideration from further biological research to the delivery of interventions. Some intriguing suggestions and pointers for the future have been described such as targeting impulsivity, risk-taking propensity, and delay discounting or choice preference. Neurobiological development of reward function is being investigated by neuroimaging studies and is a current research focus, and this may assist in the expansion of tailor-made therapies to enhance outcomes and prevent relapse. Having a greater appreciation of the specific characteristics of reward-related behavior may lead to enrichment of the socio-behavioral model by encouraging and training young people to implement coping skills by curbing self-control and impulsivity. Research on decision making, risk reduction, and behavioral control may lead to implementation of more powerful targeted interventions. While all authors agreed that there has been a wealth of research over the last couple of decades, it is essential that this is ongoing and expanded. We are aware of certain gaps, for example, the developing world, which appears to be on the cusp of the emergence of serious substance problems in its youth, has not been adequately represented.

As Dr. Chang noted in his discussion on ADHD and addiction, "Contributions from epidemiology, genetics, neuroimaging, psychopharmacology, and of course long term clinical follow up (are needed) to understand that SUD is a significant complication of the lack of adequate treatment of ADHD, often dating from early childhood," though current treatment for ADHD may not reduce this risk. He also pointed to "a bidirectional influence, especially with the use of tobacco and alcohol during pregnancy increasing the risk for development of ADHD in the fetus." This insight that the research contributions themselves need to be multidisciplinary are echoed throughout.

All authors agreed that promising interventions for adolescents who misuse substances have been identified and that we should build on findings to date to further enhance methods to improve treatment outcome, accessibility, implementation, and relapse prevention through the integration of research findings into treatment.

To conclude, as Drs. Aklin and Chambers have aptly stated:

This is of great public health importance, given the clear relationship between initiating, remaining in treatment, long-term abstinence and relapse. Developmentally appropriate, targeted treatments are likely to be more efficient and potent, require less staff time, lead to less relapse, and ultimately, reduce the burden on providers.

Adolescent and Substance Abuse

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Robert Milin and Selena Walker

Contents

Abstract

Substance use disorder (SUD) in adolescence is a serious mental health and social problem with its significant association with morbidity and mortality. Substance abuse has progressed from the more antisocial, risk-taking, and marginal groups of the population to the mainstream of society and dramatically to younger populations, reinforcing and expanding the boundaries of at-risk populations for SUD. Research in the area of adolescent substance use has expanded significantly over time, and while many studies have contributed to the growth of knowledge in this area, ongoing study remains important. Substance use may be seen through a developmental perspective progressing across adolescence into young adulthood. We have included the most recent studies and

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research findings on adolescent substance use and related disorders in this chapter. The chapter will focus on enhancing knowledge and comprehension of adolescent substance abuse in addressing the following areas: epidemiology, vulnerability and developmental course, comorbidity, assessment, treatment, and outcomes. The transitional period of adolescence presents itself as an especially critical and vulnerable time for the onset of substance use disorder (SUD) with its impact on normal development, future SUD, and for society as a whole. Adolescence is a period of major risk for the onset of SUD. Treatment approaches must be tailored to developmental patterns of substance use and include comprehensive assessment and a holistic approach. High rates of comorbid mental disorders among adolescents with SUD further emphasize the need for psychiatric care. An integrated approach to treatment for youth with SUD and comorbid mental disorders is paramount to effective intervention.

134.1 Introduction

The goal of this overview chapter is to present the current knowledge and discuss the balance of evidence to enhance the understanding, significance, and treatment of adolescents with substance use disorder (SUD). Research in the area of adolescent substance use has expanded significantly over time. While many studies have contributed to the growth of knowledge in this area, further research and study remains important. As such, we have included the most recent research and findings on adolescent substance use and related disorders in this chapter.

As preadolescent substance use is uncommon, the focus of this chapter is on the adolescent population, an age group that faces major developmental and psychosocial challenges including substance use. Substance use may result in serious mental health and social impairments with a significant association with morbidity and mortality. The onset of substance use disorder is particularly high during adolescence. Substance use has essentially become part of mainstream adolescent development and, over time, has become increasingly common among younger populations. Adolescence may be appropriately defined as a time of major risk in the development and onset of SUD.

134.2 Youth Substance Misuse

134.2.1 Epidemiology

The Monitoring the Future survey (Johnston et al. 2013) has been annually measuring the prevalence rates of substance use in adolescents attending school across the United States (US) in a nationally representative sample for more than three decades. Substance use (alcohol and illicit drugs) in general across the grades has shown a steady and measurable decline for some time led by a decline in alcohol use, though with some exceptions. The rate of binge drinking

has remained a concern at 24 % in 2012 for grade 12 students. Marijuana, in contrast, has shown a significant increase in use over the last several years affecting the rate of illicit drug use, whereas illicit drug use other than marijuana has more or less held steady or declined. The rise in marijuana use appears to mirror the lessening attitudes toward the perceived risk of harm associated with its use. The annual prevalence rates for 2012 of any illicit drug use in grades 8, 10, and 12 stand at 7.7 %, 18.6 %, and 25.2 %, respectively, which remain relatively high. Substance use overall shows a marked increase in prevalence from grade 8 to grade 12. By far, the two most common substances used by adolescents are alcohol and marijuana, with current rates for senior high school (grade 12) students of 41.5 % and 22.9 %, respectively in 2012. Marijuana has been the most common substance of daily use among adolescents by far for more than a decade, currently standing at 6.5 %. Prescription drug misuse among high school seniors remains a concern at approximately 27.7 % per annum. Included in this group are narcotic analgesics (vicodin and oxycontin), stimulants (Adderall and Ritalin) used for treatment of attention-deficit/hyperactivity disorder (ADHD), and sedatives/tranquilizers.

Prevalence rates of substance use do not provide one with comparable rates of SUD in general and especially in adolescents (American Academy of Child and Adolescent Psychiatry 2005). Substance experimentation among adolescents is highly prevalent, though the vast majority of these adolescents do not develop an SUD, even with some of these adolescents engaging in more regular use for a period of time, though the latter does increase the likelihood of developing an SUD (American Academy of Child and Adolescent Psychiatry 2005; Brown et al. 2008; Gilvarry 2000). These patterns of substance use, as it would relate to alcohol and marijuana use seen in adolescents, appear for some to be within normative behavior and part of the maturation process of adolescence, but for others may lead to significant SUD (Brown et al. 2008; Shedler and Block 1990).

The US National Comorbidity Survey-Adolescent Supplement (Merikangas et al. 2010) has recently provided us with the first general estimates of lifetime prevalence rates of SUD in this population. SUD at 11.4 % and mood disorders at 11.2 % represent the two most common categories of mental disorders with severe impairment in adolescents. It is important to recognize that the prevalence of drug use disorders at 8.9 % exceeds that of alcohol use disorders at 6.4 % contrary to adult prevalence rates for SUD. SUD was found to be somewhat more common in boys at 12.5 % than girls at 10.2 %. The median age of onset for SUD was 15 years, with a steep increase in incidence thereafter.

SUD prevalence rates have been reported in a US community sample examining higher-risk groups of adolescents receiving public sector services including those receiving mental health services. The overall past year prevalence rate for SUD was found to be 24 % across all five public sectors (Aarons et al. 2010). This rate is being more than two times greater than the recently reported prevalence of SUD in the general adolescent population.

Despite the overall relative decline of substance use in adolescents, the prevalence remains high and is the greatest with older adolescents. Emerging areas of

concern include a defined minority of adolescents who engage in polysubstance use which may carry a greater burden of related problems (Conway et al. 2013) and the rising misuse of prescription pain relievers by adolescents with evidence of significant dependence liability (Wu et al. 2008). One can also surmise that cannabis is the most telling and common substance of dependence in adolescents with alcohol being the predominant substance of abuse (Young et al. 2002; Dennis et al. 2002). The prevalence of substance use and SUD in adolescents remains a major public health issue with drug use disorders being more prevalent than alcohol use.

134.2.2 Development and Course

Levels of substance use have been found to increase from early adolescence to early adulthood (mid-1920s) and decline thereafter. Girls may exhibit higher levels of substance use than boys during early adolescence, whereas over time boys exhibit greater rates of change, resulting in high levels of substance use from mid-adolescence through young adulthood (Chen and Jacobson 2012). Adolescence is a time of major risk for the onset of SUD that shows a developmental trajectory (Palmer et al. 2009). The peak age of onset for SUD, both alcohol and drug use disorders, is in late adolescence/early adulthood, between the ages of 18 and 20 (Brown et al. 2008; Compton et al. 2007).

Adolescence, as seen from a developmental perspective, represents a time of convergence of significant neurobiological, cognitive, behavioral, emotional, and social changes with continuity of risk from earlier developmental stages, providing a unique period of heightened vulnerability and susceptibility for SUD (Brown et al. 2008; Schepis et al. 2008; Casey and Jones 2010). Brown and colleagues (2008) reflect on these interrelated developmental factors, the changes that occur during adolescence, and its influence on individual alcohol use trajectories and risk for problem drinking. The authors' narrative highlights the growing evidence that adolescents are particularly vulnerable to the adverse effects of heavy alcohol use both in the biological and social domains and that the consequences of drinking appear to differ between adolescents and adults. They also identify that problem drinking has the potential to redirect the normative course of adolescent development in a manner that increases the risk not only of alcohol use disorders but also of mental health and social problems.

Schepis and coauthors (2008) in their review of the neurobiological processes involved in the etiology of adolescent SUD emphasize the significance of maturational changes of the central nervous system that occur in adolescence, the foremost of these being synaptic pruning, myelination, and neurotransmitter system modification. In general, adolescents appear to have greater neurobiological bases for risk-taking behavior with attenuated suppressive and regulatory controls on behavior. The authors surmise that the abnormal neurological markers of those at risk for the development of SUD may best correspond to disinhibition and/or negative affect. Adolescents appear more vulnerable to the effects of many substances that are most likely mediated by increased neuroplasticity and the effects of stress. It is likely that

substance-induced neurobiological changes enhance drug use behaviors. These attributes reinforce the progression to SUD in adolescents.

A great number of risk factors have been identified in the prediction of SUD in adolescence/young adulthood. These risk factors may be conceptualized into four domains: (a) culture and society (e.g., laws and availability of substances), (b) interpersonal (e.g., peers and family including attitudes), (c) psychobehavioral (e.g., early/persistent behavioral problems, poor school performance, rebelliousness, early onset of substance use, personality characteristics such as temperament and affect), and (d) biogenetic (e.g., inherited susceptibility and psychophysiological vulnerability to the effects of substances) (Gilvarry 2000; Compton et al. 2007; Hawkins et al. 1992).

It appears that social factors, especially peer influence, are the strongest determinants of initiation of substance use, whereas psychological factors and the self-reinforcing effects of a substance are more closely associated with the progression to SUD (Newcomb 1995).

There is not much evidence to assist in distinguishing the relative importance of risk factors and their specificity in the development of adolescent SUD. It is the number of risk factors, rather than any one factor, that is predictive of SUD. Many of these risk factors are shared with those related to the onset of other mental disorders in adolescents (Gilvarry 2000; Newcomb 1995).

Protective factors are those that reduce the likelihood and level of substance use. Multiple protective factors have been identified including a positive temperament (absence of depression)/self-acceptance, intellectual ability/academic performance, supportive family/home environment, caring relationship with at least one adult, external support system (e.g., religion/church) that encourages prosocial values, and law abidance/avoidance of delinquent peer friendships (Gilvarry 2000; Newcomb 1995; Fergusson and Lynskey 1996). Again, it is not one particular protective factor but, rather, the number of protective factors that has the greatest influence on reducing the likelihood of developing SUD in adolescence. As such it has been shown that those adolescents with five or more protective factors are over 20 times less likely to develop cannabis abuse than the general sample. Protective factors also appear to have a moderating influence on the risk for drug use involvement with high protective indices being found to have the strongest effect on those at high risk for greater drug involvement (Newcomb and Felix-Ortiz 1992). One factor that has been identified above others as protective of substance use is having early academic success (Upadhyaya 2008).

The early initiation of substance use in adolescence predicts a considerably greater likelihood of developing later SUD with a more rapid progression to substance dependence, being of particular relevance for cannabis and alcohol. These findings are most robust for initiation of substance use by age 15 or younger; thereafter, other variables may come into play (Substance Abuse and Mental Health Services Administration 2009; Anthony and Petronis 1995; Chen et al. 2005; DeWit et al. 2000; Copeland et al. 2009). Adolescent SUD has been found to be a strong homotypic predictor (a disorder predicting itself over time) of young adult SUD (Copeland et al. 2009). A pattern of regular weekly use of cannabis in

adolescence appears to be a threshold marker for the risk of cannabis dependence in young adulthood (Coffey et al. 2003).

A widely held concept reasons that there are developmental stages in the progression of substance use through adolescence into young adulthood (Kandel 1975). The sequence of stages defines a temporal relationship progressing from legal to illegal and softer to harder drug use, with each stage acting as a potential "gateway" to the initiation of the next stage (Kandel 1975; Kandel et al. 1992). The use of one substance increases the likelihood of initiation of the second substance. For example, very few individuals who have tried cocaine and heroin have not already tried marijuana, the majority having previously used alcohol or cigarettes. However, the use of one substance does not invariably lead to the use of other substances. Many youth will stop at a specific stage and do not progress further or may return to an earlier stage of substance use (Kandel 1975). It is relatively common to carry over substance use from one stage to the next. Adolescents who engage in the use of multiple substances increase their risk of developing an SUD into young adulthood (Palmer et al. 2009).

The causal application of the gateway hypothesis is more open to debate and specifically as it relates to cannabis use and other drugs (Degenhardt et al. 2010). However, a strong association has been established for cannabis use and the use of other illicit drugs (Kandel 2003). Further to this, regular or heavy cannabis use has been significantly associated with other illicit drug use and abuse/dependence. The relationship is especially strong during adolescence and declines with age. These findings add support to the potential causal role of cannabis use on the development of other illicit drug use disorders, though the actual causal mechanisms, whether direct or indirect, remain unclear (Fergusson et al. 2006a, b). Adolescents may show a greater likelihood of developing drug dependence (cannabis) than adults across levels of use (Chen et al. 1997).

Substance abuse, expressly cannabis, in adolescence is clearly associated with significant developmental impairment and negative consequences in multiple life domains including behavioral, psychosocial, and academic/vocational (Brown et al. 2008; Macleod et al. 2004; Newcomb 1997; Scholes-Balog et al. 2013; Horwood et al. 2010).

In summary, the onset of SUD in adolescence with its biopsychosocial determinants is a serious mental health problem, with a serious impact on developmental tasks and a strong link to future SUD.

134.2.3 Comorbid Disorders

The association of SUD with other mental disorders is well established. In clinical and treatment studies of adolescent SUD, elevated rates of comorbid mental health disorders have been found across clinical settings with prevalence rates ranging from 55 % to 80 % (Clark et al. 1997; Dennis et al. 2004; Sterling and Weisner 2005; Stowell and Estroff 1992). Prevalence rates of comorbid disorders are significantly greater than community control samples of non-SUD adolescents.

Adolescent SUD patients often present with more than one comorbid disorder. Clinical studies, however, may suffer from Berkson's bias where it is probable that an adolescent with a particular disorder such as SUD who is seeking treatment will have a greater likelihood of a second disorder, thus confounding the ability to generalize results. Only a handful of studies have examined the comorbidity of adolescent SUD in general community samples. Two such studies have found similar elevated rates of comorbidity as seen in clinical studies. Comorbidity rates were two to three times greater in adolescents with SUD than those without SUD for anxiety, mood, or disruptive behavior disorders (DBD). In comparison to adult studies, comorbidity rates of mental disorders are similar for lifetime SUD and may be higher for current SUD in adolescents (Kandel et al. 1999; Rohde et al. 1996). These higher rates of psychiatric comorbidity in adolescents with SUD are most likely reflective of the number of DBD diagnoses made in adolescents that are either not applicable to or not routinely assessed for in adults. There is some evidence to support that comorbidity of mental disorders increases with progression of SUD and severity of substance use (Grella et al. 2001; Tims et al. 2002). The genders share far greater similarities than any meaningful differences with respect to comorbidity characteristics, especially when gender differences seen in the general population of such disorders as conduct disorder (CD) and major depressive disorder (MDD) are taken into account (Dennis et al. 2004; Armstrong and Costello 2002).

Prospective studies suggest that early and more frequent substance use through adolescence is associated with, and may predict, later mental disorders in particular depressive disorders in young adulthood (Brook et al. 2002, 1998; Hayatbakhsh et al. 2007). Analysis of retrospective epidemiologic data has found the age of onset of DBD and anxiety disorders to precede the onset of substance dependence (Glantz et al. 2009).

The most common comorbid mental disorders seen in community studies of adolescent SUD are that of DBD, in particular CD, with these disorders showing a prevalence range of 25–50 % and a median of four times greater likelihood of co-occurrence with SUD than without. The next most common comorbid disorder is that of depressive disorders with a prevalence range of 20–30 % and a median of over twice the likelihood of co-occurrence (Armstrong and Costello 2002). These findings are relatively consistent with clinical studies, though there is a fair degree of variability in prevalence rates between studies of clinical population samples. On the other hand, SUD is a common comorbid disorder in clinical studies of youth that present with serious emotional problems or mental disorders (Deas 2006; Greenbaum et al. 1991; Grilo et al. 1995; Kramer et al. 2003).

In this section of comorbidity, we will take a closer look at selected aspects of the relationship of the more prominent comorbid mental disorders and SUD.

134.2.3.1 Conduct Disorder

CD and SUD are strongly associated, with CD typically preceding the onset of SUD (Costello et al. 2003; Grilo et al. 1996; Sung et al. 2004). CD imparts an increased risk for the initiation of substance use by age 15 and is a powerful prediction of

SUD by age 18 (Hopfer et al. 2013; Elkins et al. 2007). As well, the severity of CD has been found to predict the severity of SUD. This relationship, however, appears to be reciprocal with each condition heightening the expression of the other. In such a manner, early-onset substance use has been associated with later criminality, and if substance use or drug dealing is reduced, there is a subsequent decrease in criminality (Stein et al. 2008).

Adolescents who present with CD may rapidly progress from substance use initiation through abuse to dependence, moving from one stage to the next in a matter of months (Reebye et al. 1995), whereas early conduct problems have not been directly linked to the onset of SUD in adulthood (Milin et al. 1991). Also, juvenile offenders with comorbid SUD have shown greater additional psychopathology than those without SUD (Milin et al. 1991).

134.2.3.2 Attention-Deficit/Hyperactivity Disorder

ADHD has been found to be a common comorbid disorder in clinical studies of adolescents with SUD, with large outpatient clinical studies reporting a range of 17–38 %; however, similar findings have not been found in community samples (Dennis et al. 2004; Sterling and Weisner 2005; Armstrong and Costello 2002; Disney et al. 1999).

There has been considerable debate in the extant literature as to whether ADHD is an independent risk factor for the development of SUD in youth or whether the association is indirect and mediated by the presence of co-occurring CD or oppositional defiant disorder (ODD) (Brook et al. 2010; August et al. 2006; Barkley et al. 2004; Biederman et al. 1997). What is now clearer on the balance of evidence is that childhood ADHD is a risk factor for the development of SUD in young adulthood, independent of co-occurring ODD/CD with the dimension of hyperactivity/impulsivity being of particular significance. However, the addition of ODD/CD and severity of ADHD further increases the risk for SUD in youth (Elkins et al. 2007; Wilens et al. 2011; Charach et al. 2011; Molina and Pelham 2003). Adolescents with ADHD have shown an earlier age of onset of SUD, a more rapid progression of SUD, and a greater severity of SUD (Biederman et al. 1997; Horner and Scheibe 1997).

Considerable evidence exists as supported by a recent meta-analysis that treatment of childhood ADHD with stimulant medication does not increase the risk of SUD in adolescence or young adulthood (Mannuzza et al. 2008; Biederman et al. 2008; Wilens et al. 2003, 2008; Barkley et al. 2003; Molina et al. 2013; Humphreys et al. 2013). There has also been a certain degree of evidence to suggest that stimulant treatment of ADHD may even reduce the risk of developing SUD in adolescence, though the effect appears to wane into young adulthood (Biederman et al. 2008; Wilens et al. 2003, 2008; Katusic et al. 2005). However, more recent research findings have not been supportive of a protective stimulant treatment effect for the risk of adolescent or later SUD (Molina et al. 2013; Humphreys et al. 2013).

The relationship between ADHD and SUD remains complex in adolescence, and with the addition of CD, this grouping of disorders may represent a worse prognosis for the persistence of antisocial behaviors and substance abuse.

134.2.3.3 Depressive Disorders

Depressive disorders frequently co-occur with adolescent SUD and are the second most common comorbid disorder. The association of depressive and substance use disorder in adolescents is more frequent than one would expect and has been more widely studied than other comorbidities. It is also noteworthy that adolescents with a history of MDD show an elevated rate of SUD than those without a history of depression (Substance Abuse and Mental Health Services Administration 2009; Rao et al. 1999). Rao and Chen (2008) in a comprehensive review of this topic proposed that common genetic, environmental, and neurobiological factors may possibly mediate the relationship between depressive and substance use disorder in adolescents, constituting a basis for their linkage. The authors recognized the limitations of the neurobiological findings and, by design, the selectivity of various risk mechanisms examined.

In clinical studies of adolescents with SUD, the onset of MDD most often follows the onset of SUD (secondary MDD). Secondary MDD is considerably more common than MDD preceding the onset of SUD (primary MDD) (Bukstein et al. 1992; Deykin et al. 1992). In the majority of cases, irrespective of whether it is primary or secondary, comorbid MDD in adolescents has not been found to spontaneously remit with abstinence and/or early treatment (excluding pharmacotherapy) by the third week. As would be expected, comorbid MDD has been found to be more prevalent in girls with adolescent SUD than in boys, with the girls showing an earlier age of onset of depression (Deykin et al. 1992). Adolescents with SUD and comorbid depressive symptoms on admission to residential treatment have shown poor substance use outcome (Subramaniam et al. 2007).

Adolescents with depression are more likely to develop an SUD, showing an earlier onset and a greater severity of substance abuse. Comorbid SUD in adolescents with depression appears to have a negative impact on the phenomenology and course of illness with greater behavioral and CD problems, longer duration of depressive episodes, and increased psychosocial (school, family, and legal) impairment (Rao et al. 1999; Rao and Chen 2008; Subramaniam et al. 2007; King et al. 1996, 1993). A greater severity of substance use in adolescents with treatment-resistant MDD (without comorbid SUD) has been associated with increased severity of depression and comorbid ODD and CD. Adolescents with low substance-related impairment at the end of treatment for depression showed the best response (Goldstein et al. 2009). Alternatively, achieving a positive response in the treatment of adolescents with MDD has been shown to reduce the risk of subsequent drug use disorders but not alcohol use disorders (Curry et al. 2012).

SUD in adolescents has been linked to an increase in suicidal behaviors including ideation, attempts (frequency, recurrence, and seriousness), and completed suicide. However, the risk for suicide is most significant when comorbid with MDD (Crumley 1990; Brent et al. 1993; Esposito-Smythers and Spirito 2004).

The comorbidity of substance use and depressive disorders appears to be interactive and has at least an additive, if not a synergistic effect on the burden of illness of these disorders, with significant morbidity and mortality.

134.2.3.4 Psychotic and Bipolar Disorders

Few studies report an incidence of comorbid psychotic and bipolar disorders in the adolescent SUD population. This absence of reporting is quite likely a reflection of the severity of the illnesses, with those adolescents who experience the onset of these disorders being more likely to present to psychiatric services for assessment irrespective of whether they have an SUD or not. In that comorbid psychotic and bipolar disorders are not commonly or reliably reported in the adolescent SUD population, only a few selected comments will be made in this chapter.

A strong association has been found for comorbid SUD with first-episode psychosis (FEP) and bipolar disorder (BD) in adolescents/young adults. The presence of comorbid SUD has been associated with a more debilitating course of illness, poorer clinical and treatment outcomes, as well as greater functional impairment in patients with FEP and BD (including evidence in first-episode mania and adolescents) than without comorbid SUD. SUD has been linked to an earlier age of onset of schizophrenia and BD with its significant negative clinical implication on prognosis. In the majority of cases, SUD typically precedes the onset of psychosis/schizophrenia, whereas the onset of BD may often precede that of SUD. The most common SUD is that of cannabis in FEP and first-episode/early-onset BD (Milin et al. 2010).

Cannabis use has been found to be an independent risk factor for the development of psychosis/schizophrenia in young adulthood with a two- to threefold increase in risk. The risk for this outcome increases in a dose-dependent manner and is greater with the onset of use in adolescence and especially in vulnerable individuals. Cannabis-induced psychotic disorder has been found to be a cogent marker in the vulnerability for developing a primary psychotic disorder. In essence, adolescents and young adults should be counseled that cannabis use may increase their likelihood of developing a clinically relevant psychotic disorder/schizophrenia-related disorder (Milin et al. 2010; Moore et al. 2004; Large et al. 2011).

134.2.3.5 Other Comorbid Disorders

There is considerably less extant literature on the relationship of other comorbid disorders in adolescents with SUD. Elevated rates of anxiety disorders, including social and generalized anxiety disorders and posttraumatic stress disorder (PTSD), have been noted in clinical studies (Sterling and Weisner 2005; Crumley 1990; Brent et al. 1993; Esposito-Smythers and Spirito 2004; Giaconia et al. 2000). From these studies, social anxiety disorders (SAD) and PTSD have been identified as the most clinically relevant of the anxiety disorders. SAD precede the onset of SUD and inherently may have an impact in SUD treatment that is oriented toward group therapy. Those with SAD may best be served initially through individual cognitive behavior-oriented SUD treatment.

The relevance of PTSD in this population is significant, given the high rate of physical and sexual abuse (57 % of girls and 31 % of boys) identified in a clinical sample across treatment settings (residential, inpatient, and out-/day patient programs) (Rounds-Bryant et al. 1998). In a cross-sectional community sample of

adolescents, a strong association was found for the comorbidity of SUD and PTSD with a significant impact on psychosocial impairment. The findings suggested multiple pathways leading to comorbid SUD and PTSD (Abrantes et al. 2003).

No consistent association has been found in adolescents for comorbid SUD and eating disorders (ED). There is some clinical evidence to suggest a possible relationship of SUD with bulimia (Von Ranson et al. 2002).

134.2.4 Assessment of Adolescent Substance Use Disorder

It is recommended by both the American Academies of Child and Adolescent Psychiatry and Pediatrics that screening for substance use and SUD in adolescents be part of standard clinical care (American Academy of Child and Adolescent Psychiatry 2005; Committee on Substance Abuse 2011). It has also been asserted that the goal is to apply universal screening for substance use, brief intervention, and/or referral to treatment (SBIRT) for every adolescent on an ongoing basis as part of routine healthcare, employing developmentally appropriate tools and strategies (Committee on Substance Abuse 2011). However, further study of long-term effectiveness of SBIRT in the adolescent population is required (Pilowsky and Wu 2013). Despite the importance of screening adolescents for substance use, most physicians/pediatricians feel uncomfortable screening for drug and alcohol use, and even fewer feel comfortable completing a comprehensive assessment or referring adolescents for drug and alcohol treatment (Van Hook et al. 2007). Reasons for failure to screen adolescents for substance use and abuse include the lack of training and familiarity with screening tools, time to complete the assessment, need to triage competing medical problems, unfamiliarity with treatment options and resources, and issues with confidentiality and disclosure due to parents who will not leave the room (Van Hook et al. 2007).

Screening tools are brief self-reports or interviews often used as the initial step in assessing for adolescent substance use and related problems. The outcome of screening may determine the need for further evaluation and a more comprehensive assessment. The next step would entail a comprehensive assessment that examines the severity and course of substance use and related problems (frequency, quantity, duration, number of substances used and circumstances, etc., problem-related consequences of substance use and treatment needs in multiple life domains (Winters and Kaminer 2008)). The appropriateness of the instrument is dependent upon the setting and the purpose of the assessment (Samet et al. 2007). Winters and Kaminer (2008) identified and reviewed several preferred measures for screening and assessing adolescent SUD in clinical populations. Their selection of instruments was comprised of two screening tools, the CRAFFT and the Personal Experience Screening Questionnaire, and three comprehensive assessment instruments, the Global Appraisal of Individual Needs (GAIN), the Teen Severity Addiction Index, and the Personal Experience Inventory. These instruments were guided by a combination of robust psychometrics and user-friendliness. The features they examined included the strength of psychometric properties, simplicity of

scoring, efficient length of administrations, and the degree of user training required. The measures were also found suitable for periodic use in reevaluation of treatment outcome. The authors recommend that clinicians working with youth should receive training in at least one screening and one comprehensive assessment instrument, ideally during their formal years of education (Winters and Kaminer 2008). The CRAFFT has been identified as the best studied screening tool for substance use and related problems in adolescents with evidence to support its use in medical settings (Pilowsky and Wu 2013).

Urine drug testing is an objective measure to screen for recent drug use in a time-limited manner. However, a positive urine screen is not diagnostic of an SUD and does not provide information on substance-related problems. Echoing the findings from studies investigating the concordance between objective, self-, and collateral reports of substance use in adolescents (Winters et al. 2008; Burleson and Kaminer 2006), Winters and Kaminer (Winters and Kaminer 2008) advocate that the use of self-report and collateral information may be the most reliable measure in many instances of assessing adolescent substance use and disorders. Nevertheless, urine drug analysis may be beneficial when screening those who fear the consequences of reported substance use and abuse or those who are concerned about confidentiality and therefore may not respond validly. As well, it may be helpful as a tool in providing clinical feedback to the adolescent in treatment and in assessing clinical response to treatment.

The significance of screening and assessing for SUD in adolescents using multiple sources is brought to bear by findings from a study of adolescents seeking mental health treatment (Kramer et al. 2003). SUD prevalence was found to be approximately 17 % on a self-report structured measure, whereas clinicians identified less than half (45 %) of these adolescents with SUD. The researchers suggested that the gap between the need and access to SUD treatment services may have contributed to poorer outcomes for youth with comorbid SUD. They also noted the important clinical consideration that clinicians should continue to screen/assess for SUD throughout treatment in that confidence to disclose this behavior may be enhanced with the establishment of a therapeutic relationship with the adolescent patient and family.

In summary, there is convincing evidence that all adolescents seeking treatment for essentially any condition should, at minimum and in an ongoing manner, receive screening for substance use and as warranted more comprehensive assessment for SUD. Assessment should include diverse sources where possible and cover multiple life domains leading to identifying the appropriate treatment resources to meet the needs of the adolescent.

134.2.5 Treatment

Treatment of adolescent SUD starts for all intents and purposes with the process of a biopsychosocial/multidimensional assessment (Ahuja et al. 2013). The American Society of Addiction Medicine Patient Placement Criteria (ASAM-PPC) for the treatment of substance-related disorders (American Society of Addiction

Medicine 2001) sets forth consensus criteria and guidelines for adolescents with many distinguishing features from that of adults. The six dimensions identified for assessment include (a) intoxication and withdrawal potential; (b) medical conditions and complications; (c) emotional, behavioral, and cognitive condition (includes stages of development) and complications; (d) readiness for change; (e) relapse, continued use, or problem potential; and (f) recovery environment.

The evaluation of key clinical domains within dimension (c) is intended to help guide the clinician with treatment planning and toward matching the adolescent patients to the appropriate level of care. ASAM-PPC has become a standard in the addiction field in the United States. Unfortunately, only preliminary work has been done in the study and operationalization of the adolescent PPC (Fishman 2008).

An area often previously overlooked in adolescents is the presence of substance withdrawal and its impact. Recent studies support that cannabis withdrawal is common and of clinical significance in adolescents with cannabis dependence (Milin et al 2008; Cornelius et al 2008).

The treatment of adolescent SUD may occur at one of several levels of care, across a range of settings reflecting the intensity of treatment and level of supervision/restriction of environment (American Academy of Child and Adolescent Psychiatry 2005). These treatment settings mainly encompass outpatient, partial hospitalization/day treatment, and inpatient or residential care. There continues to be a significant gap between adolescents who need treatment for SUD and those who receive treatment in a specialty facility. It is likely that two major factors play a role in this marked deficit of treatment: they did not seek treatment or they were unable to access treatment for various reasons (Substance Abuse and Mental Health Services Administration 2009).

As of date, there has been a proposed shift away from large-scale outcome-based performance measurements as they may be impractical where outcomes may be reflective of case mix, and between program differences may be small, for identifying quality of care indicators for adolescent SUD treatment programs (Morral et al. 2006). Along these lines, Brannigan and colleagues (2004) identified several key elements of effective adolescent drug treatment through literature review and expert panel consensus. The key elements identified were (a) assessment and treatment matching, (b) comprehensive integrated treatment approach, (c) family involvement, (d) developmentally appropriate program in treatment, (e) engaging and retaining teens in treatment, (f) qualified staff, (g) gender and cultural competence, (h) continuing care, and (i) treatment outcomes. However, no weighting was assigned to these key elements. In a subsequent survey of highly regarded adolescent SUD treatment programs across a range of settings in the United States, most were found to be insufficiently undertaking the key elements of effective adolescent SUD treatment in their programs. The elements with the poorest quality performance were assessment and treatment matching, engaging and retaining teens in treatment, gender and cultural competence, and treatment outcomes. The authors concluded that there is a considerable need to expand the awareness of effective elements in treating adolescent SUD and that this will heighten program improvement and also serve as a measurement of progress in the field.

In reviews of studies on adolescent SUD treatment outcomes, it can be derived that treatment is better than no treatment (American Academy of Child and Adolescent Psychiatry 2005). The largest follow-up study to date of over 1,000 adolescent patients, SUD treatment outcomes across different treatment modalities [outpatient, short-term inpatient, and residential care] showed significant improvements in the domains of substance use, psychological adjustment, school performance, and criminal behavior at 1 year posttreatment than in the year prior to treatment. Also, a longer duration of treatment was associated with reduced rates of substance use and a decrease in arrests following treatment. These findings are similar to those in adult SUD treatment evaluation research as well as the finding that different treatment modalities appear to reflect different levels of problem severity (Hser et al. 2001).

134.2.5.1 Psychosocial Treatments

Waldron and Turner (Waldron and Turner 2008) undertook a comprehensive review and meta-analysis of psychosocial outpatient treatment modalities for adolescent SUD with the purpose of establishing evidence-based practice guidelines. They identified three approaches to be considered as well-established interventions: the first two being family-based approaches, multidimensional family therapy (MDFT) and functional family therapy, and the third being group cognitive behavioral therapy (CBT). The authors also found other family models, including multisystemic therapy, brief strategic family therapy, and behavioral family therapy, as most likely efficacious, pending further exploration by independent researchers. Both Adolescent Community Reinforcement Approach (ACRA) and other individual CBT models appear promising but require further research. They also concluded that none of the treatment approaches emerged as being superior over another. Subsequent to this meta-analysis of psychosocial outpatient treatments for adolescent SUD, further studies have supported the benefit of individual CBT (Cornelius et al. 2009; Riggs et al. 2011). Also, findings for the effectiveness of MDFT have been replicated in a RCT of adolescents in Western Europe, showing a reduction of the rate of cannabis dependence (Rigter et al. 2013). In a comparative analysis of outpatient treatment effectiveness for adolescent substance abuse, psychoeducational therapy did not fare well as compared to other treatments (Tanner-Smith et al. 2013).

Waldron and Turner (2008) also identified Winters and colleagues' evaluative study of the Minnesota Model 12-step approach for treatment of adolescent SUD as promising, with favorable substance use outcomes, and worthy of further research to establish the effectiveness of this treatment approach. The Minnesota Model has been reported to be the most widely used approach in the United States for the treatment of severe SUD/substance dependence in adolescents which is typically conducted in a short-term (28-day) admission to a specialized inpatient hospital or residential care setting. An intensive day treatment program was also included as part of Winters and colleagues' study which showed similar treatment outcome findings to short-term residential care (Winters et al. 2000).

To date, the largest randomized adolescent SUD treatment study has been the Cannabis Youth Treatment (CYT) study (Dennis et al. 2004). This multisite

comparative study ($N = 600$) was comprised of two interrelated randomized trials of five short-term psychosocial treatment interventions for outpatient adolescents with cannabis use disorders. Comorbidity was common with 33 % of the adolescents having internalizing disorders and 60 % presenting with externalizing disorders. All interventions were designed to be developmentally appropriate. The study included an extended period of naturalistic follow-up of more than 8 months posttreatment, with study completion at 12 months postrandomization to treatment. All five CYT interventions, including brief psychotherapy of five sessions in total, were found to be effective, demonstrated by significant improvements in the days of abstinence by an average of 24 % and the percent of adolescents in recovery (no substance use or abuse/dependence problems) averaging 24 % across the 12-month duration of the study. Clinical outcomes were similar across treatment sites and interventions, with no significant differences between conditions on these outcome measures. Despite the findings of clinical improvements, more than 50 % of adolescents went in and out of recovery or relapse one or more times posttreatment. The majority were still reporting substance use or related problems at 12 months. These results lead the authors to suggest a need to consider the potential role of continuing care for a significant segment of adolescents entering outpatient treatment for SUD.

134.2.5.2 Treatment Outcome Parameters

A substantive concern has been the high rates of attrition reported in adolescent SUD treatment that ranges from 20 % to greater than 50 % across program types (Chung and Maisto 2006; Monti et al. 2001). This high rate of treatment dropout is greater than that seen in adults and is likely related to the adolescents' typically low motivation for treatment and the absence of perceiving their substance use as a problem. The CYT study (Tims et al. 2002) reported that only 20 % of adolescents who entered treatment viewed their substance use as a problem. There has been no thorough examination of motivation as a moderator of treatment outcome in adolescents. However, along this line of thinking, several psychosocial interventions for adolescent SUD have specifically incorporated individual motivational enhancement therapy (MET) as part of treatment (Waldron and Turner 2008). Recent studies have demonstrated in several modes of treatment that formation of early therapeutic alliance predicts the likelihood that adolescents will stay in treatment and that they will have better clinical outcomes on measures of drug use as well as internalizing and externalizing behaviors (Waldron and Turner 2008; Diamond et al. 2006).

Most adolescent SUD treatment programs advocate a primary goal of achieving and maintaining substance abstinence. The maintenance of abstinence has been linked to positive long-term psychosocial functioning in treated youth (Brown et al. 2001). Reviews of adolescent treatment outcome studies identify relatively low rates of continuous abstinence following treatment with over 50 % of adolescents showing relapse of substance use by 3 months posttreatment (Chung and Maisto 2006; Williams and Chang 2000). In comparison to adults, the rates and timing of relapse to any substance use posttreatment appear to be similar. However, the most

common context for initial relapse differs between adolescents and adults. Adolescents most commonly report a social situation or peer influence such as socializing with pretreatment friends as context for initial relapse, whereas adults most commonly report negative intra- or interpersonal states (Chung and Maisto 2006).

Follow-up treatment studies that examine the patterns of substance use suggest fluctuations in use and problems with an overall reduction of clinical symptoms in youth who have received treatment (Chung and Maisto 2006). The reduction in substance use and improvement in related problems are appropriate measures of treatment outcome. Predictors of adolescent SUD treatment outcome have been historically categorized into pretreatment, in-treatment, and posttreatment determinants.

Pretreatment factors, in general, represent background and personal characteristics that, upon entering treatment, may be associated with outcome. Multiple pretreatment characteristics have been identified as potential variables that may have an impact on outcome, but study findings and the manner of reporting factors associated with treatment outcomes are inconsistent. However, a few pretreatment determinants are worth considering, these being severity of substance use, school functioning, and social supports. Demographic characteristics of gender and ethnicity, overall, have not been found to predict outcome.

The in-treatment factors most consistently associated with favorable treatment outcomes are treatment completion, with its correlation to programs that provide comprehensive services, and longer time in treatment. Posttreatment factors include a wide range of psychosocial and environmental variables that occur following treatment that may influence outcomes. Posttreatment factors most consistently related to positive outcome include, but are not limited to, participation in aftercare treatment, peer/parental social support, and prosocial activities. As expected, posttreatment factors have been found to be the most important determinant of clinical outcomes (American Academy of Child and Adolescent Psychiatry 2005; Chung and Maisto 2006; Williams and Chang 2000; Anderson et al. 2007). More recently, the literature on adolescent SUD treatment has emphasized the need for evaluation of both moderators and mediators of specific treatment interventions that may affect outcome. Moderators are pretreatment characteristics that influence the association between treatment intervention or other independent variables and treatment outcome. Mediators are intervening determinants that may account for the association between a treatment intervention and outcome (Waldron and Turner 2008).

A better understanding of the impact of risk and protective factors on substance-related outcomes improves the ability to enhance treatment and relapse prevention programs (Anderson et al. 2007). For example, in an adolescent treatment outcome study, persistent cigarette smokers and smoking initiators during the follow-up period of 1 year were found to be significantly at greater risk for relapse of any substance than those who quit smoking or were non-smokers. The implications of this study would be to incorporate smoking cessation treatment in the context of adolescent SUD treatment and relapse prevention programs (de Dios et al. 2009).

Several adolescent SUD studies have identified the impact of psychiatric comorbidity on treatment outcomes across treatment modalities (residential, short-term

inpatient/residential care, and outpatient programs). In general, those adolescents with mixed comorbidity of both internalizing and externalizing disorders or with a greater number of comorbid mental disorders showed an increased rate/level of substance relapse/use. Findings from certain studies have supported a more rapid time to relapse of substance use than those adolescents without comorbidity at treatment follow-up of 6 or 12 months (Grella et al. 2001; Rowe et al. 2004; Tomlinson et al. 2004; Shane et al. 2003). The majority of adolescents with comorbidity in these treatment studies presented with both comorbid internalizing and externalizing disorders. In an adolescent SUD treatment study that investigated the impact of internalizing and externalizing behaviors on clinical outcomes over both short-term (1 year) and long-term (4 and 5.5 years) follow-up, it was found that adolescents with externalizing behaviors had significantly more rapid and higher rates of substance relapse as well as lower treatment retention than those with internalizing behaviors. The authors concluded that these results suggest poorer prognostic treatment outcomes for youth who show core features of delinquency or deviant behavior (Winters et al. 2008).

Comorbid CD has been implicated in poorer SUD treatment outcomes. Kamon and colleagues (2005), in an open study involving a family-based contingency management model including individual CBT, provided support for the feasibility and potential for improved retention, substance use outcomes, and reduction of conduct problems in adolescents with SUD (all met criteria for cannabis use disorder), who received this intervention.

134.2.5.3 Aftercare Treatment

There is a paucity of studies examining the effectiveness of continuing care (CC) in adolescents who have received SUD treatment. Godley and colleagues (2002) provided preliminary evidence in their randomized study to support the role of assertive continuing care (ACC) involving case management and ACRA over referral to CC as usual for adolescents discharged from residential SUD treatment. Adolescents who received ACC were more likely to show greater initiation and retention in CC and improved short-term substance use outcomes in comparison to those referred for CC as usual. Adolescents who receive residential SUD treatment often have the most serious SUD and are at high risk for relapse.

Kaminer and colleagues (2008) conducted the first and what would appear to be the *only* published prospective randomized controlled trial (RCT) of active aftercare intervention (five in-person or brief telephone sessions) in outpatient adolescents with AUD. The adolescents were identified for the study as having alcohol use disorders (AUD) and completed outpatient group CBT treatment for SUD with aftercare intervention being delivered in the first 3 months posttreatment. Adolescents who received aftercare were significantly less likely to experience relapse to alcohol use versus those who did not receive aftercare, despite the overall significant increase in relapse occurrence at the end of aftercare compared to the end of treatment. The authors concluded that active aftercare posttreatment was relatively efficacious but that the dose of aftercare may not have been sufficient to maintain treatment gains.

134.2.5.4 Pharmacotherapy for SUD

Open-label studies of naltrexone and ondansetron treatment for adolescents/youth with alcohol dependence have shown a reduced frequency of alcohol use (Deas et al. 2005; Dawes et al. 2005). In an open study and a case series of naltrexone and extended release naltrexone, respectively, in youth with opioid dependence both showed a reduction in frequency of opioid use (Fishman et al. 2010).

Youth with opioid dependence participated in a randomized double-blind parallel group clinical trial of buprenorphine ($n = 18$) or clonidine ($n = 18$) for detoxification over 28 days (Marsch et al. 2005). Irrespective of group assignment, all youth received counseling and contingency management. The researchers reported significantly greater treatment retention and greater number of negative opioid urine screens for those youth who received buprenorphine than for those who received clonidine. Following detoxification, youth were offered to continue treatment for opioid dependence with naltrexone. Sixty-one percent of the youth from the buprenorphine group and 5 % of those from the clonidine group opted to initiate treatment with naltrexone. The authors concluded that buprenorphine as an adjunct to behavioral therapies was a more effective intervention than clonidine in combination with behavioral therapy (Marsch et al. 2005).

Treatment-seeking youth with opioid dependence ($N = 152$) participated in a randomized clinical trial (RCT) of 12 weeks of buprenorphine–naloxone treatment ($n = 74$) or short-term (14 days) detoxification ($n = 78$) in addition to weekly group and individual counseling (Woody et al. 2008). Woody and colleagues reported significantly greater numbers of negative opioid urine screens at weeks 4 and 8 for youth who received buprenorphine–naloxone compared to short-term detoxification. Greater treatment retention at week 12 was found for the youth in the buprenorphine–naloxone treatment group in comparison to those youth who received short-term detoxification. Follow-up at months 6, 9, and 12 found that those youth who had received buprenorphine–naloxone treatment had fewer positive opioid urine screens than those adolescents who had received short-term detoxification, although rates were high for both groups (Woody et al. 2008).

A small RCT ($N = 26$) of acamprosate treatment for 90 days in adolescents with alcohol dependence reported the number of youth continuously abstinent, and the number of continuous days abstinent was greater in the acamprosate group than those in the placebo group (Neiderhofer and Staffen 2003).

Gray and colleagues investigated the benefits of n-acetylcysteine (NAC), in an eight-week double-blind RCT ($N = 116$) of cannabis-dependent youth who also were receiving weekly contingency management and brief cessation counseling (Gray et al. 2012). The authors found that youth in the NAC group had a greater than twofold likelihood of a negative cannabis urine screen compared to those youth in the placebo group at treatment end. At 4 weeks posttreatment follow-up, youth who had received NAC did have a greater frequency of negative urine screens than those who had received placebo, but the difference was not statistically significant.

All of these studies reported pharmacotherapy in the context of concurrent psychosocial or behavioral therapies for SUD. The exact role of each therapy cannot

be determined definitively. Furthermore, due to methodologic differences in research studies, results may not be replicable and are not directly comparable, rendering it difficult to assess the preference of one pharmacotherapy over another. Nevertheless, the limited research suggests a certain advantage for those using pharmacotherapy in the treatment of adolescent substance dependence, in conjunction with either psychosocial behavioral therapy, in particular for opioid dependence.

In a case series study by Duffy and Milin (1996) of withdrawal syndrome in adolescents with cannabis dependence, the authors commented on the clinical utility of using trazodone 50–100 mg at bedtime to assist with withdrawal insomnia. Since then, our center has also found quetiapine 50–100 mg at bedtime to be helpful for cannabis withdrawal insomnia in outpatients. Research studies are required to investigate whether selective pharmacotherapy may be beneficial in the management of cannabis withdrawal symptoms and enhance rates of discontinuation of cannabis dependence in adolescents.

134.2.5.5 Pharmacotherapy for Comorbid Disorders

A small randomized, pilot study of sertraline in outpatient adolescents with alcohol dependence and comorbid clinical depression showed that both groups (sertraline and placebo) experienced a reduction in number of drinking days, a reduction in depression scores, and no significance between group differences. These results may have been due, at least in part, to the requirement that all subjects received CBT regardless of group membership, suggesting the potential effectiveness of CBT in treating MDD and alcohol dependence (Deas et al. 2000).

A small open trial of fluoxetine in adolescents with comorbid MDD, SUD, and CD who were in residential treatment for SUD found promising results. Subjects were included in the study if their depression persisted after at least 1 month of residential care and they were abstinent from substance use (Riggs et al. 1997). The findings showed an improvement of depressive symptoms and functioning. Cornelius and colleagues (2005) examined the effectiveness of fluoxetine, in an acute open-label trial and 5-year naturalistic follow-up study of a small group of adolescents with comorbid AUD and MDD who also received treatment as usual, individual psychotherapy, over the acute phase of the study. The acute-phase study results showed a significant reduction (improvement) in depression symptoms and alcohol use. In the 5-year follow-up phase of the study, the subjects (who were now young adults) continued to maintain improvements in depressive symptoms although recurrent episodes were common, and comorbid AUD continued to improve over the course of follow-up.

To date, the largest published RCT of pharmacotherapy in adolescents with comorbidity ($N = 126$) evaluated the efficacy of fluoxetine and individual CBT for SUD in adolescents with MDD, SUD, and CD (Riggs et al. 2007). Riggs and coauthors reported that fluoxetine combined with CBT had demonstrated greater efficacy on one of the two depression response measures with a significantly greater reduction in depressive symptoms than placebo and CBT. Both treatment groups demonstrated a higher-than-expected rate of treatment response, which suggested to the researchers that CBT may have contributed to this occurrence with mixed

efficacy results. There was an overall decrease in substance use and CD symptoms in both conditions but no between-group differences were found. It was also reported that those adolescents or those who experienced remission of MDD had a greater proportion of negative results on weekly urine drug screens and self-reported days of drug use in the past month, compared to those without remission, irrespective of treatment group assignment. In terms of clinical implications, the authors proposed that the study findings showed that in the context of CBT for SUD, comorbid depression may improve or remit without antidepressant pharmacotherapy. However, if depression does not appear to be improving early in the course of SUD treatment with CBT, then fluoxetine treatment should be considered even if the adolescent is not abstinent, with careful follow-up monitoring of adherence and progress in treatment.

A subsequent RCT in adolescents ($N = 50$) with comorbid MDD and AUD also investigated the efficacy of fluoxetine treatment with all subjects receiving individual manualized CBT, for the treatment of MDD and AUD, and manualized MET for SUD. Cornelius and colleagues (2009) found no significant treatment outcome differences between the fluoxetine and placebo treatment groups. Both treatment groups showed significant improvements in alcohol use and depressive symptoms over the duration of the study, with having received a course of CBT/MET therapy. The number of heavy drinking days was significantly associated with the lack of remission of self-reported depressive symptoms. The study results lead the researchers to consider various reasons for their findings including limited medication efficacy, small sample size, the efficacy of CBT/MET psychotherapy, and to some extent depressive symptoms that may have been alcohol/substance induced. They suggested that psychological intervention should be the first line of treatment in this adolescent comorbid MDD/AUD population with pharmacotherapy afforded to those adolescents who do not respond to psychosocial intervention alone (Cornelius et al. 2009). In commentary, the findings of these two RCTs of fluoxetine/placebo and CBT add to the evidence of the effectiveness of individual CBT as a treatment intervention for adolescents with SUD and especially for those adolescents with comorbid MDD.

Only one RCT study of adolescents with BD and comorbid SUD has been conducted. Geller and colleagues (1998) in a small RCT ($N = 25$) examined the efficacy of acute lithium treatment in outpatients presenting with bipolar spectrum disorders and comorbid substance dependence with all subjects receiving interpersonal therapy. The lithium treatment group demonstrated a reduced number of positive drug urine screens and an improvement of general psychopathology on a measure of global assessment in comparison to those receiving placebo. However, no between-group differences were found on measures of mood or substance dependence symptoms. Nevertheless, the authors concluded that lithium was an effective treatment for both disorders. Though often reported in the literature, this study has numerous limitations, and there have been no further published trials to replicate or build on the findings.

In a community study, adolescents with ADHD and comorbid SUD and CD participated in an RCT ($N = 69$) to evaluate the effectiveness of

pemoline treatment (Riggs et al. 2004). The study results demonstrated a significant improvement in the severity of ADHD symptoms for the pemoline group as compared to the placebo group. No significant differences were found between the two groups on measures of substance use or conduct symptoms that did not differ from baseline scores. This study was unique as no concurrent psychosocial SUD treatment was provided. The authors concluded that pemoline was efficacious for ADHD but lacked effect on symptoms of CD and SUD in the absence of specific treatments for SUD, supporting the clinical importance of treating comorbid ADHD in the context of concurrent SUD treatment.

A small 6-week crossover ($N = 16$) in adolescents with ADHD and SUD who received treatment with methylphenidate-SODAS, a long-acting formulation, demonstrated a significant reduction in ADHD symptoms and improvement of clinical global functioning versus placebo. There was no significant treatment effect on substance use including no increase in substance use with this long-acting treatment (Szobot et al. 2008).

In a larger RCT ($N = 70$) of atomoxetine for ADHD in adolescents with SUD where all subjects received MET/CBT for SUD, no between-group differences were found for ADHD or substance use. However, both groups, atomoxetine plus MET/CBT and placebo plus MET/CBT, showed a significant reduction in ADHD symptoms. The authors concluded that MET/CBT and/or a placebo response contributed to a high treatment response in the placebo group for ADHD, although substance use findings were more equivocal (Thurston et al. 2010).

Riggs and colleagues (2011) completed a multisite community-based 16-week RCT of OROS methylphenidate, an extended release formulation, in 303 adolescents with SUD and comorbid ADHD who were also receiving CBT. All youth, regardless of treatment arm (OROS methylphenidate and CBT or placebo and CBT), had significant improvements in ADHD symptoms and a significant reduction in substance use at study end, although no significant differences were found between those youth who received OROS methylphenidate and those who did not. The authors concluded that there was no greater efficacy for OROS methylphenidate over placebo for either symptoms of ADHD or decrease in substance use for youth receiving individual CBT for concurrent SUD and ADHD. Adolescents who received OROS methylphenidate and CBT, however, had significantly fewer positive urine drug screens than those who received placebo and CBT (Riggs et al. 2011). An important clinical consideration in the selection of these medications for the treatment of comorbid ADHD in adolescents with SUD has been the understanding that they carry low abuse liability.

In summary, over the last decade, there have been significant advances in the development of evidence-based psychosocial treatments for adolescent SUD in outpatient settings. These fall within the broad categories of family-based interventions and developmentally appropriate CBT as well as the assimilation of MET as part of these interventions. There is accumulating evidence that supports the benefit of adolescent SUD treatment programs across different settings, including residential, short-term residential/inpatient, partial hospitalization/day treatment, and outpatients, as well as some promising findings with respect to aftercare.

It is well defined that treatment of comorbid mental disorders in adolescent SUD remains a priority and a necessity to enhance treatment effectiveness. Pharmacotherapy for the treatment of adolescent SUD remains a work in progress, especially with respect to the direct treatment of substance dependence. At this point, the effectiveness of pharmacotherapy for such common comorbid disorders as MDD and ADHD has not been established in the context of adolescents with active substance dependence. There are mixed findings whether concurrent pharmacotherapy of these comorbid disorders may be beneficial from the onset of treatment in the framework of evidence-based psychosocial therapy for adolescents presenting with SUD.

The current clinical implication being that concurrent pharmacotherapy for comorbid disorders may be best served for those adolescents engaged in SUD treatment who show persisting symptoms of MDD or ADHD with significant reduction in substance use/abstinence. Apart from the need for larger treatment studies, there is also the need for extended or maintenance pharmacotherapy trials in adolescents with SUD and comorbid disorders.

134.3 Conclusion

In sum, SUD among adolescents has multiple implications on normal development, future SUD, and for society in general. Adolescence is a period of significant vulnerability and risk for the development of SUD; as such, SUD must be viewed from a developmental perspective. Treatment approaches must be tailored to developmental patterns of substance use and include comprehensive assessment and a holistic approach. High rates of comorbid mental disorders among adolescents with SUD further emphasize the need for psychiatric care. Thus, an integrated approach to treatment focusing on SUD and comorbid mental disorders is paramount to intervention.

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Suicide and Substance Abuse in Adolescents

135

Dan Shlosberg and Gal Shoval

Contents

Abstract

Suicide is the second or third leading cause of death among adolescents in the industrialized world. Adolescent suicidal behaviors pose a major global public-health concern since they are highly prevalent and associated with heavy mortality and morbidity. A plethora of data accumulated substantiates the connection between suicide and substance abuse in adolescents and poses substance use disorders as a major risk factor for emergent suicidal behaviors. This chapter reviews the recent patterns and trends of substance abuse, focusing mainly on alcohol and cannabinoid-based substances which are most prevalent among adolescents, and presents the existing evidence linking adolescent suicidal behavior and substance abuse. We address the role of salient moderating factors such as comorbid psychiatric pathologies, age, and gender differences on

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this relationship and highlight vulnerable subpopulations such as sexual minorities that are predisposed to be affected by this connection. Perspectives on recent as well as future basic science research studying the connection between adolescent suicide and substance abuse are discussed. Current treatment strategies for substance use disorders as well as for suicidal behaviors are presented, arguing in favor of an integrated approach.

135.1 Introduction

Suicidality is a broad term encompassing a wide range of self-injurious ideation or self-inflicted harmful behaviors executed with at least a partial intent to die. These behaviors are a major global public-health concern since they are highly prevalent and associated with heavy mortality and morbidity in the immediate as well as in long term. This issue is intensified when child and adolescent suicidality is concerned, and therefore, a pressing demand for efficient prevention plans and novel treatment strategies yet remains.

Suicide is a complex behavior and various pathways lead to suicidality. Numerous risk factors associated with suicidality have been described (Bursztein and Apter 2009; Cash and Bridge 2009) and are frequently divided into several categorical groups. This reductionism in classification of suicidality risk factors can be misleading and in many cases not clinically pragmatic. In real-life situations, these risk factors are much too often interwoven (Wolitzky-Taylor et al. 2010), are mutually effective in a nonadditive and unpredictable manner, and ultimately pose a methodological conundrum in the clinical assessment of adolescent suicidality. Nevertheless, in epidemiological studies concerning suicidality, several risk factors including substance use disorders (SUD) stand out more prominently than others.

Much epidemiological data has been gathered in the past decades elaborating the details and extent of adolescent substance use. The information accumulated has been extensively used recently by various health services as well as clinicians to yield a plethora of studies substantiating the impact of SUD on adolescent suicidality. In recent years, one can witness a gradual transformation of the harnessed data from the descriptive to the operative form; suicide risk assessments and odds ratios are being translated into operational plans and large-scale screening and intervention efforts in schools and health facilities. The applicability and efficacy of these measures are yet to be ascertained and validated by evidence-based studies.

Although the boundaries between substance use, abuse, or dependence are clearly defined by DSM criteria, these terms will be interchangeably used in this text as to keep with the general idea of defining the effect of substance use on suicidality and not to constrict this effect in boundaries of time, quantity, level of impairment, and related pathologies. Since the scope of this chapter cannot encompass the specific effect of all illicit as well as legal substances on suicidality, we will focus mainly on alcohol and cannabinoid-based substances since these are the substances which are most widely used and studied worldwide (NSDUH 2012a; UNODC 2012).

135.2 The Multifaceted Relationship Between Suicide and Substance Use

135.2.1 Adolescent Suicidality

There are multiple levels of severity and injury burden within the construct of "suicidality." The scope of suicidal behavior constrained in this term ranges from *suicidal ideation* with or without a specific plan through *suicide attempt* which is a nonfatal, self-inflicted destructive act with explicit or inferred intent to die to finally the fatal act of a completed suicide (O'Carroll et al. 1996).

Suicide is the second or third leading cause of death among adolescents in the USA and Europe (CDC 2013a; Eurostat 2013), and suicidal behavior represents one of the greatest public-health issues for this population. Lifetime estimates of suicide attempts among adolescents range from 1.3 % to 3.8 % in males and 1.5 to 10.1 % in females (Bridge et al. 2006). These numbers should most probably be considered to underestimate the true extent of this malady; a large portion of suicidal attempts remain unnoticed and unreported since most data rely on self-report or emergency-department (ED) admissions. Indeed ED visits in the USA due to self-inflicted injury are highest among the 15–19-year-old age group, and the visit rate in this group has doubled in the past 16 years (Ting et al. 2012). In the USA, youth risk behavior surveys (YRBS) assessing health-risk behaviors among youth and young adults have been conducted among representative samples of high school students biennially since 1991 by a nationwide Youth Risk Behavior Surveillance System (YRBSS). The latest survey released in 2012 reports disconcerting data describing teenage suicidal behavior. During the 12 months prior to the survey, 15.8 % of students had seriously considered attempting suicide, 12.8 % had formulated a suicide attempt plan, and 7.8 % had reportedly attempted suicide one or more times, an alarming rise from the prior survey reporting 6.3 % (Eaton et al. 2012). Adolescent suicidality has been identified as a nationwide health improvement priority in the USA. The "healthy people 2020 (HP2020)" initiative has proposed the objective of reducing adolescent suicide attempt rate by 10 % (healthypeople.gov) in the next decade. Given a 27 % decrease in adolescent suicide rate in the previous decade, this goal does not seem unattainable. In 2011, 2.4 % of US high school youth made a serious suicide attempt (resulting in an injury, poisoning, or overdose that had to be medically treated), a rise from 1.9 % recorded in the previous report (Eaton et al. 2012); in order to achieve the HP2020 goal, this number has yet to decrease to 1.7 %.

In light of these figures and those of previous years, numerous suicidality detection and prevention strategies have been proposed and implemented to various degrees of success worldwide (Mann et al. 2005). Most adolescents presenting with suicidal behavior do not end up committing suicide; nevertheless, suicidal ideation in adolescence has been shown to be a harbinger of compromised adult functioning and future axis I diagnoses (Reinherz et al. 2006), stressing the need for early suicidality identification regardless to the obvious dire consequences of suicide itself. In their review of the latest suicidality screening tools applied in educational and health-related community facilities, Horowitz et al. (2009) suggest that the

implementation of targeted suicide screening in schools and universal suicide screening in primary care clinics and ED may be the most effective way to recognize and prevent suicidal behavior. The leading screening tool used today in school settings is the Columbia Suicide Screen (CSS) (Shaffer et al. 2004). This short self-report measure embedded in a general health questionnaire addresses known suicide risk factors such as suicidal ideation, prior suicide attempts, depression, anxiety, and substance use. Those who screen positive in the initial stage progress to treatment referral following clinical confirmation of suicidality. It has been recently shown that by selectively setting the threshold of the algorithm that picks out the initial target cases, it is possible to minimize the false-positive cases that burden the screen site with secondary interviews while allowing a minimal loss of true positive cases (Scott et al. 2010). Another screening tool that is not specific to suicide or substance abuse is the Strengths and Difficulties Questionnaire (SDQ) (Goodman 1997), which has the advantage that it can detect adolescent emotional and behavioral difficulties that are not necessarily strictly DSM based and therefore may be more sensitive to detect distress and psychopathology (Shoval et al. 2013).

Recent encouraging data suggest a decrease in global adolescent suicide rate. A significant linear decrease in the prevalence of US adolescents having made a suicide plan has been noted in the past 20 years (18.6 to 12.8 %), although no significant change occurred in the prevalence of actual attempts (Eaton et al. 2012). During the past decade, the crude death rate from suicide and intentional self-harm among adolescents aged 15–19 residing in the 27 countries of the European Union has also dropped from 6/100,000 people to 4.6/100,000 (Eurostat 2013).

135.2.2 Adolescent Substance Use

135.2.2.1 Alcohol Use

Adolescent alcohol use is related to the three leading death causes in the young (Naso et al. 2008), namely, accidents, suicide, and homicide. These three death causes account for approximately 75 % of all mortality cases between ages 15 and 24 (NVSR 2013), and therefore, alcohol is related to most premature death cases in the young. The use of alcohol increases the likelihood of violent deaths including suicide in direct (acute intoxication) as well as indirect (loss of inhibition, increased impulsivity) means. Most of completed suicide cases are indirectly rather than directly linked to alcohol use. In American youth under 21 years old, an annual average of 480 deaths due to suicide are attributable to excessive alcohol use (CDC 2013b), whereas only a small minority of adolescent suicide cases (4 %) are directly induced by ingestion of alcohol or drugs (NVDRS 2013). A high prevalence of up to 45 % of alcohol involvement has been found in adolescent hospital admissions due to physical trauma (Sindelar et al. 2004).

Alcohol use has been shown to be associated with elevated rates, and increased risk for adolescent suicidality (Borowsky et al. 2001; Esposito-Smythers and Spirito 2004; Kokkevi et al. 2012) even after the effects of depression, impulsivity, peer delinquency, and parental monitoring are controlled for (Swahn et al. 2008). But although

alcohol abuse is strongly related to suicidality, the proof of causality between the two in adolescents is not as evident (Pompili et al. 2010). Patterns of alcohol "use" or "abuse" can vary widely in terms of time (e.g., how many days in a month) and volume (e.g., how many drinks each time), and so it may be more appropriate to examine the association with suicidality in instances in which alcohol is consumed in excess. Consuming five standard alcoholic drinks or more in the same drinking session ("binge drinking") would cause most adolescents to reach at least some degree of intoxication. Although no cross-country or cultural consensus exists to define an alcohol volume of a standard drink or how many drinks constitute a "binge," binge drinking can generally be viewed as a rapid consumption of alcoholic beverages with the intention of becoming intoxicated. On average, nearly half of the students in the USA (54 %) as well as in Europe (47 %) reported that they had been intoxicated in this sense at least once during their lifetime (Hibell et al. 2012; Johnston et al. 2013).

Binge drinking, otherwise known as "heavy episodic drinking," represents a pattern of alcohol consumption which is highly associated with health risks (Miller et al. 2007). It is most prevalent among teenage alcohol consumers and is associated with increased risk for suicidal thoughts and attempts, even when compared to current alcohol drinkers who do not binge drink (Miller et al. 2007). This connection is strongly correlated to frequency of binging; those who binge on more than 10 monthly occasions attempt suicide more than those who binge six to nine times (30 % vs. 16 %) and almost three times as much as those who binge once a month (11.9 %) (Miller et al. 2007).

Binge drinkers tend to explore the use of other psychoactive substances, some of which are associated with increased suicidality risk. Current heavy episodic drinking shows a significant correlation to lifetime use of cannabis (Hibell et al. 2012). Also, adolescent alcohol binge drinking carries an odds ratio (OR) of 60 for concurrent marijuana use as compared to nonalcohol drinkers, much more than that of alcohol drinkers who do not binge ($OR = 5$) (Miller et al. 2007). Adolescents reporting concurrent alcohol and marijuana use presenting to the ED following alcohol intoxication display heavier drinking patterns as compared to those who report alcohol use alone, including increased binge drinking instances as well as elevated alcohol consumption on each drinking occasion (Chun et al. 2010).

Recently Archie et al. suggested that binge drinking raises the risk for suicidality in youngsters only when depression is present (Archie et al. 2012). Using a survey delivered to over 17,000 adolescents aged 15–24 years, they show that binge drinkers and non-binge drinkers shared the same risk for suicidality when no depression was present even when using more stringent definitions of binge drinking (at least once weekly). When the effect of depression was tested, they found that depressed binge drinkers had an increased risk for suicidality as compared to non-binge drinkers who were not depressed ($OR = 6.3$) (Archie et al. 2012). Similar results have also been reported recently for adults (Shoval et al. 2014).

It is generally perceived that in countries in which alcohol per capita consumption is high, binge drinking is low ("social drinking" countries). Indeed, some of the developed West European countries display the most substantial adult per capita consumption rates while also displaying the least risky patterns of alcohol

consumption and a relatively decreased net alcohol-attributable mortality rates (WHO 2013). This perception may very well be true for the adult population, but not necessarily so for adolescents. Data analysis from recent large-scale surveys reports that regular alcohol use does not predict low levels of binge drinking. In fact, no correlation was found between the proportion of students in a country who had been drinking during the past 30 days (current users) and the amounts consumed on the latest drinking day (Hibell et al. 2012). It is thus important not to rely on common notions and beliefs regarding adolescent alcohol consumption patterns, which may be quite unpredictable and unsimilar to adult patterns of alcohol use.

The criteria for alcohol abuse and dependence needed to establish the DSM-IV diagnosis of alcohol use disorders should be viewed carefully when addressing adolescents vs. adults since there are important developmental differences in the clinical characteristics of alcohol use disorders in adolescents and adults (Perepletchikova et al. 2008). Of the seven DSM-IV-TR criteria defining alcohol dependence, for example, the emergence of "withdrawal" is more rare among adolescents, and the behavioral correlates of "tolerance" and "drinking more than intended" criteria are frequently endorsed by adolescents with low levels of alcohol consumption and problem severity (Chung et al. 2005). Winters et al. recently suggested several targeted adjustments to the upcoming DSM-5 diagnostic criteria of SUD so as to make them more applicable to the adolescent population and to ensure the validity of the diagnosis across developmental stages (Winters et al. 2011). Specifically they proposed the exclusion of the "hazardous use" criterion from the "alcohol abuse" diagnosis, reasoning it is highly associated with automobile use which is more applicable to adult behavior. They also advocated adolescent-targeted adjustments to be made for the definitions of "tolerance," "withdrawal," and the DSM-5 "craving" criteria, all of which are influenced by developmental changes. Finally, during DSM-5 discussions, it was proposed to raise the diagnostic threshold for SUD in order to avoid unnecessary labeling and stigmatization of mild or intermittent cases.

Treatment options for alcohol disorders are markedly more abundant today than were in the past. In their review of the various assessment instruments and treatment options currently in use for alcohol use disorders in youth, Perepletchikova et al. suggest Multidimensional Family Therapy (MDFT) and group-administered Cognitive Behavioral Therapies (CBT) in combination with brief individual Motivational Enhancement Therapy (MET) as the most evidence-based supported treatment strategies of adolescent alcohol use disorders (Perepletchikova et al. 2008). A recent study suggested that MDFT may be superior to other strategies in youth presenting with more severe drug use and greater psychiatric comorbidity (Henderson et al. 2010). Although this study performed a secondary analysis of two randomized controlled trials whose subjects were primarily diagnosed with cannabis use disorders and were not suicidal, a substantial minority had an alcohol use disorder and so these results may also be highly relevant to adolescents suffering from alcohol use disorders as well.

135.2.2.2 Trends in Alcohol Use

Adolescent alcohol use in the USA is steadily declining. In 2011, 70.8 % of high school students reported they had ever drank alcohol, a decrease from 81.6 % just two decades ago (Eaton et al. 2012). A drop of more than 20 % in the corresponding years has been demonstrated in youth reporting current alcohol use, from 50.8 % to 38.7 % (Eaton et al. 2012). Data from the ongoing Monitoring the Future (MTF) study corroborate these findings. The latest report presenting adolescent alcohol use has reached a historic low, from 93 % lifetime prevalence of use in senior year high school students 30 years ago down to 50 % today (Johnston et al. 2012). The situation in European countries is quite different; adolescent alcohol use has remained relatively unchanged in the past 15 years. The European School Survey Project on Alcohol and Other Drugs (ESPAD) which is based on data from more than 100,000 European students from 36 countries reports that for youth averaging 15.8 years of age, lifetime use of alcoholic beverages has dropped only slightly from 89 % in 1995 to 86 % in 2011 (Hibell et al. 2012). As can be expected, substantial prevalence differences were found between countries in this study. Although these figures probably reflect different social and cultural norms in drinking patterns, the different rates of decline in adolescent alcohol consumption might also reflect the utility of various alcohol-use prevention plans locally employed. Many educational and preventive policies aimed to reduce the harmful use of alcohol have been formulated and utilized worldwide in the past three decades (WHO 2013) and the use of alcohol in adolescents as aforementioned is since on the decline. Furthermore, temporal trend reports of American adolescent binge drinking prevalence present a 30 % decrease from 1991 to 2011 (31.3–21.9 %) including an impressive 50 % decline in male binge drinking since 1981 (Johnston et al. 2013), perhaps reflecting the success of educational preventive strategies focusing on the behavioral aspect of alcohol use (highlighting negative aspects of "drunkenness" instead of "drinking") and not of restrictive strategies (e.g., increased legal drinking age). It is also debatable whether restrictive measures for alcohol use are applicable, alcohol is perceived by youth to be easily available, and four in five students (81 %) find it fairly or very easy to get hold of an alcoholic beverage (Hibell et al. 2012). Strict policies may also lead to rebellious behavior and an increased prevalence of binge drinking. A recent study exploring the drinking pattern and drunkenness among mid-adolescents in 40 European and North American countries found a trend whereby higher prices and stronger alcohol controls were associated with a lower proportion of weekly drinking but a higher proportion of drunkenness (Gilligan et al. 2012).

Nevertheless, in summary, alcohol remains the substance most widely used today by teenagers, and seven out of every ten students have consumed alcohol by the end of high school (Johnston et al. 2012). Given the close association to suicidality, this should warrant continuing efforts to decrease adolescent alcohol use and not to rejoice over the positive statistical data reporting its decrease.

135.2.2.3 Cannabinoids Use

The US nationwide MTF study utilizes national samples of 45,000–50,000 students in three grades (8th, 10th, and 12th) that have been surveyed every year since 1991 (Johnston et al. 2013). In 2012, the percentages of students indicating any use of an illicit drug in the prior 12 months (representing current users) were 13 %, 30 %, and 40 % in grades 8, 10, and 12, respectively. The percentages indicating any use during their lifetime were 19 %, 37 %, and 49 % (Johnston et al. 2013). Data concerning drug use in European countries has also been gathered in the past two decades and summarized in the ESPAD report. Latest prevalence reports of lifetime drug use were on average 21 % for boys and 15 % for girls (Hibell et al. 2012); clearly these numbers stand out as modest compared to those in the USA.

These differences persist when focusing on current cannabis users alone; the annual prevalence rate in the USA in 2012 was 28 % for 10th graders (Johnston et al. 2013), while the ESPAD reported 13 % prevalence for the corresponding age group (Hibell et al. 2012). According to the latest YRBS report, 23.1 % of high school students had used marijuana on one or more occasions during the 30 days prior to the survey (Eaton et al. 2012), much more than the 7 % reported by European students (Hibell et al. 2012). It is of note in this context that the ESPAD also gathered data from US students and presented lower prevalence data than did the YRBS (18 % use in the prior month) (Hibell et al. 2012).

While cannabinoids by far represent the most prevalent illicit substance group for adolescent use today, data regarding the prevalence of other illicit drugs can be found elsewhere (Hibell et al. 2012; Johnston et al. 2013; NSDUH 2012a) but will not be elaborated here in detail. Briefly, about 4 % of adolescents aged 12–17 years in the USA report the current use of illicit drugs excluding marijuana. Of the several illicit substance groups whose prevalence has been annually monitored, the illicit use of psychotherapeutics (including amphetamines, sedatives, tranquilizers, and narcotics) is second to marijuana, while hallucinogens, inhalants, and other drugs are far less prevalent. The National Survey on Drug Use and Health (NSDUH) obtains information from approximately 70,000 US residents aged 12 years and older regarding several categories of illicit drug use. In the latest report relating to 2011, about half (47.7 %) of youths aged 12–17 reported that it would be "fairly easy" or "very easy" for them to obtain marijuana if they wanted (NSDUH 2012a); indeed, the rate of current marijuana use among this age group remained unchanged in the past decade (8.2 and 7.9 % in 2002 and 2011, respectively) (NSDUH 2012a). But although these numbers imply an apparent stagnancy in the effectiveness of drug prevention programs, the comparison of adolescent marijuana use trends with their reported perception of risk from its use reveals that this may not be so. It is interesting that as the rates of adolescents' perception of "great risk of harm" due to regularly smoking marijuana decreased between 2007 and 2011 (from 54.6 % to 44.8 %, respectively), the rate of its current use increased from about 6.7 % in 2007 to 7.9 % in 2011 (NSDUH 2013). The analysis of the temporal trends suggests that the implementation of education programs directed to specifically explicate the dangers associated with substance use may be useful and so should be continuously encouraged since perception of risk of harm

from marijuana reversely correlates to its use. However, since marijuana use has recently been on the rise, further improvement of these educational programs in warranted.

It is worth mentioning that temporal changes in patterns of adolescent substance abuse clearly exist, stressing the importance of ongoing efforts to monitor drug-use trends. For instance, the use of nonmedical analgesic opioids has recently become second in prevalence to marijuana, surpassing the use of inhalants and hallucinogens (Wu et al. 2011). Recently, the rise in adolescents' use of synthetic cannabinoids has also become a source of major concern due to high rates of reported use and its relative ease of availability. Youth aged 12–17 account for the highest rate of ED visits involving synthetic cannabinoids (DAWN 2012), and its annual prevalence among American 12th graders in 2012 was 11.3 % (Johnston et al. 2013). This high prevalence rate is alarming considering the intensive federal and state efforts to reduce its use. A comprehensive national US ban enacted in July 2012 might decrease the prevalence of this drug group among adolescents. There are no studies yet linking suicidality and synthetic cannabinoids use in adolescents. As clinical observations of their rapid growth of use and harm accumulate in our mental health center, our group is currently designing such a study.

135.2.3 Substance-Related Disorders as a Risk Factor for Suicidality

The link between substance use and suicide among adolescents is well established by evidence from clinical and epidemiological studies (Pompili et al. 2012; Swahn et al. 2012; Wilcox 2004; Wolitzky-Taylor et al. 2010). Moreover, drug and alcohol abuse are strong predictors of reattempting suicide within 12 months (Vajda and Steinbeck 2000). Postmortem examination studies lend further proof to this relationship; one of these studies reported that in pediatric (<19 year) decedents tested positive for illicit drugs, 93 % died from violent causes and of these 15 % had committed suicide (Naso et al. 2008).

Importantly, the strength of this connection appears correlated to the severity level of suicidal behavior. For instance, adult suicide completers are significantly more likely to use alcohol or drugs prior to their suicidal attempt than suicide attempters (DeJong et al. 2010). Moreover, suicide attempters are more likely to be substance dependent than suicidal ideators (Gould et al. 1998; King et al. 2001), suggesting that substance use may in fact facilitate the escalation from ideation to behavior. In a large study among 15,885 French adolescents (Huas et al. 2008), 32 % used cannabis at least once during their lifetime. Of these, 16 % were considered "former users" since they had not used cannabis in the prior month and 8 % others had used cannabis less than six times during that time period and were considered "occasional users," while those using cannabis over six times were deemed "heavy users." In this study, the risk for suicide attempt was 30 % higher among "heavy users" than "occasional users," clearly strengthening the notion of a positive correlation between cannabis use patterns and suicide attempts.

Interestingly, the OR for suicide attempt was $OR = 4.2$ for the "occasional users" and $OR = 2.9$ for the "former users" as compared to "nonusers." In light of the general opinion that the adverse psychosocial effects of cannabis stem from frequent use alone, the finding that the risk for suicidality is also related to occasional and even sporadic use is noteworthy. The causative correlation in the opposite direction between suicidality and the degree of substance use is not as clear. A recent study set out to investigate the relationship between suicidal ideation and cannabis use using data gathered from a 30-year longitudinal study of a birth cohort. Using a statistical model, they show that cannabis use may lead to suicidal ideation in susceptible subjects, but more importantly, that suicidal ideation does not lead to cannabis use (van Ours et al. 2013).

Regarding drug use habits associated with "more of others" as contrary to "more of the same" pattern, polydrug consumption is highly correlated to increased suicide risk. In a recent large European sample of over 45,000 adolescents from 16 countries, the percentage of respondents who reported at least one suicide attempt increased sharply with the number of substances used. Logistic regression analysis revealed that the risk for suicide attempt was $OR = 4.47$ for users of two substances and continued to increase thereafter with the use of additional substances as compared to nonusers (Kokkevi et al. 2012). Quite contrarily to popular belief, regular cannabis use does not substitute or protect from the use of other illicit drugs, rather it is strongly associated with their later use ("gateway drug") in an age-dependent manner (Fergusson et al. 2002). Since adolescent polydrug use is a widespread phenomenon and is most severe among drug abusers (EMCDDA 2009), prevention and treatment strategies should pay specific attention to this subpopulation.

Substance abuse in youth suicide attempters does not appear to conform to socioeconomic boundaries. Reported levels of substance abuse among youth patients presenting with suicidality to EDs in either an academic medical center located in west Los Angeles (LA), California, or a county hospital in southern LA were similar, although many disparities were found between the two locations regarding sociodemographic and background statistics (Asarnow et al. 2008). The effect of substance use on suicidal behavior may be so strong to a degree that it even may reverse social-cultural norms. A national American study of Latino adolescents revealed that immigrant generation status (foreign-born immigrants vs. later US-born generations) was a determinant for suicide attempts, problematic alcohol use, and repeated marijuana and other drug use. In this study the authors describe that first-generation youth were less likely to attempt suicide compared with second- and later-generation youth. They also found a marked linear relation between immigrant generation status and both illicit drug use and problematic alcohol use. Using path analysis, they propose that repeated non-marijuana drug use mediates the effect of generation status on the propensity to attempt suicide (Pena et al. 2008).

Despite drug surveillance programs as well as prevention and intervention strategies applied, the risk of suicidality associated with drug abuse in adolescents remains stable in the past two decades and still poses a major public-health concern.

Recently, using nationally representative samples of adolescents aged 12–17 years recruited and interviewed in two waves in 1995 and 2005, Wolitzky-Taylor et al. presented a dramatic decrease in suicidality risk associated with depression or alcohol abuse, whereas the risk attributable to substance abuse remained constant throughout these years (Wolitzky-Taylor et al. 2010).

135.2.4 The Moderating Role of Psychiatric Morbidity

SUD and suicidality are both highly associated with additional psychiatric comorbidity (Armstrong and Costello 2002; Foley et al. 2006). Unfortunately, the moderating effect of psychiatric comorbidity on the relationship between them is highly complex and hard to clarify. For instance, adolescent SUD patients display high psychiatric comorbidity most commonly associated with externalizing disorders (Armstrong and Costello 2002; Couwenbergh et al. 2006), whereas suicidal adolescents also tend to display psychiatric comorbidity though mainly with internalizing disorders (Foley et al. 2006; Kelly et al. 2004). The presence of a psychotic disorder also displays a moderating effect on this relationship; Shoval et al. presented a significant and strong association between suicide attempts and the use of illicit substances among adolescent suicidal inpatients diagnosed with schizophrenia or schizoaffective disorder as compared to non-suicidal patients (Shoval et al. 2006). The presence of personality disorders (PD) or traits may further intricate the assessment of this connection. Most patients diagnosed with a PD that perform completed suicidal acts (Fleischmann et al. 2005) as well as those who are diagnosed with SUD (Pereiro et al. 2013) are reported to fall into the antisocial or borderline PD classification. It is of importance, however, to note that many studies do not assess or report the presence of PD at all but instead focus on axis I diagnoses.

Not only the nature of the psychiatric disorder present but also the number of concurrent psychiatric disorders may increase the risk for suicidality. In a prospective study investigating suicidality among 180 discharged adolescent psychiatric inpatients followed for up to 13 years, most of those who were suicidal during the follow-up period had concurrent depressive disorders, and many had also displayed disruptive behavioral disorders either alone or concurrently (Goldston et al. 2009). In the same line of evidence, Vander et al. have shown that co-occurring depression and conduct disorder symptoms increase the risk for subsequent suicidality as compared to a single diagnosis of either of these (Vander et al. 2011).

Kelly et al. investigated the effects of psychiatric disorders on suicide attempts among 503 adolescents diagnosed with SUD (Kelly et al. 2004). By comparing non-suicidal to suicidal adolescents, they revealed that concurrent diagnosis of major depression or bipolar disorder conveyed the highest risks for attempting suicide. They also showed that attention-deficit hyperactivity disorder (ADHD) was associated with increased risk for male-attempted suicide, while conduct disorder was associated with attempted suicide among females. Regression hazard

analysis revealed that adolescents with SUD were most likely to attempt suicide when they also had a concurrent mood disorder (Kelly et al. 2004).

135.2.4.1 Mood Disorders as a Model

An estimated two million American youths suffer annually from a major depressive episode (8.2 % of the population aged 12–17) (NSDUH 2012b), and depression is the strongest known risk factor for adolescent suicide (Asarnow et al. 2008; Brent et al. 1993; Shaffer et al. 1996; Wolitzky-Taylor et al. 2010). Recent data suggest that even subthreshold depression, which is highly prevalent and can be found in up to 30 % of adolescents, is associated with increased suicidality risk (Balazs et al. 2013). A simplistic view would hold that the identification of adolescents prone to or suffering from depression should decrease suicidality following their adequate treatment; apparently, this is not as simple as one may reason. An ongoing debate exists regarding the effects of antidepressant on suicidality. Some evidence suggest that antidepressant medication by itself may increase the risk for adolescent suicidal behavior (Hetrick et al. 2012; Schneeweiss et al. 2010), while other studies provide evidence for an adolescent suicidality-lowering effect of antidepressants (Kuba et al. 2011; March et al. 2007). Currently most clinicians agree that treatment benefits outweigh the risks (Bridge et al. 2007).

Adolescent depression displays high comorbidity with alcohol and substance abuse (Armstrong and Costello 2002; Sher and Zalsman 2005). Adolescents suffering from major depressive episodes (MDE) were found to be more likely than those without past year MDE to have used illicit drugs in the past year (36 % vs. 17.4 %) or to be heavy alcohol users in the past month (2.5 % vs. 1.4 %); this disparity increases when comparing rates of substance dependence or abuse (NSDUH 2012b).

The combination of adolescent depression and substance abuse has been shown to elevate the risk for suicidality (Kovacs et al. 1993; Levy and Deykin 1989). This may be true even for mild to moderate substance abuse and subthreshold to diagnostic criteria of SUD (Huas et al. 2008).

Some studies reveal a synergistic effect when comorbidity occurs. For instance, the combination of depressive symptoms and problem drinking in adolescents has been shown to convey a stronger risk for suicidal behavior than problem drinking or depressive symptoms alone (Windle and Windle 1997). This effect on the suicidal risk may be mediated by substance-induced increased impulsivity. Interestingly, this synergism may disappear in the transition to adulthood since in adults with MDE, alcohol dependence does not significantly affect the risk for suicidality (Shoval et al. 2014).

The causative relationship between substance abuse, depression, and suicidality remains unknown. Studies that address this relationship face many methodological challenges (Galaif et al. 2007). A fundamental impediment is that both depression and substance abuse are independently highly associated with adolescent suicidality and their co-occurrence is the rule rather than the exception in adolescents. Large-scale prospective studies addressing this causative connection may aid the construction of suicide screening and prevention strategies. For example, Goldstein et al. used post hoc analyses on data from the Treatment of SSRI-

Resistant Depression in Adolescents (TORDIA) study to demonstrate that the level of substance-related impairments is reversely correlated to the response to antidepressive treatment (Goldstein et al. 2009), suggesting that treating substance abuse may by itself decrease depression and suicidality.

Data concerning suicidality in other mood disorders associated with substance use comorbidity are scarce in the adolescent population and usually hampered by a retrospective design. Most clinicians thus rely on adult studies and execute data extrapolation when considering risks and prevention plans. Nevertheless, the connection between bipolar disorder (BD) and suicidality has been demonstrated in many retrospective studies (Brent et al. 1988; Goldstein et al. 2005, 2008). Recently, a study designed to assess predictors of prospectively observed suicide attempts among youth with bipolar disorder revealed a strong association of this disorder with high rates of suicide attempts (Goldstein et al. 2012). This study utilized subjects enrolled in the Course and Outcome of Bipolar Youth (COBY) study and is the first prospective-designed study to date testing the BD-suicidality connection in adolescents. During the 5-year follow-up period of 413 adolescents diagnosed with BD, 76 (18 %) attempted suicide once or more. Of these, 31 attempted suicide more than once for a total of 163 suicide attempts during the follow-up period. Considering the early mean age of the study recruits (12.6 years), these figures may underscore the actual suicide attempt rate since most of these adolescents had yet to pass through the highest risk period for new onset of suicidal behavior (age range, 16–18 years (Kessler et al. 1999)).

The strength of the BD-suicidality connection may be correlated to the severity of suicidal behaviors. Brent et al. described an extremely high prevalence of BD in adolescent suicide completers. The diagnosis of BD (either type I or II) in suicide completers (22 %) was found to be at least four times more prevalent than in suicidal inpatients admitted for attempted suicide or for having a suicidal ideation (Brent et al. 1988). Surprisingly, suicide completers in this study did not display a higher frequency of the co-occurrence of mood disorder and substance abuse than non-completers. Though in a consequent larger sample study (Brent et al. 1993), they show that substance abuse is a more significant risk factor for suicide completion when comorbid with a mood disorder than when alone ($OR = 17.0$ vs. 3.3). Other studies describe the negative effect of substance use on suicidality in BD; Goldstein et al. reveal a double risk for SUD and lifetime excessive drinking in BD-diagnosed adolescents who concomitantly performed a suicidal attempt as compared to those who did not. During the 8 weeks prior to the attempt, the risk for SUD was tripled (Goldstein et al. 2012). The same group reported that in a large sample of bipolar adolescents in which lifetime prevalence of SUD was 16 %, subjects with SUD demonstrated a significantly greater lifetime prevalence of suicide attempts as compared to those without SUD (Goldstein et al. 2008).

Interestingly, the effect of substance abuse and in particularly that of cannabinoids on suicidality in BD patients may be exacerbated by the emergence of increased psychotic features (Henquet et al. 2005; Wolitzky-Taylor et al. 2010), which have been shown to increase suicidality in pediatric BD (Caetano et al. 2006). Most recently, adolescent high-risk offsprings of BD patients were

compared by a lifetime diagnosis of SUD. Those with a lifetime SUD had a significantly higher likelihood of meeting criteria for a lifetime major mood episode and a significantly higher risk of having experienced clinically significant psychotic symptoms. Consequent predictive models displayed a direct connection between SUD and emergent psychotic features (Duffy et al. 2012).

The rate of suicide attempts in youths with BD-I has been shown to be higher than in youths with BDII (Goldstein et al. 2005). In a retrospective study by Sublette et al. SUD was associated with suicide attempt in BD-I but not BD-II adults (Sublette et al. 2009). In this study the presence of both alcohol and drug use disorders increased the odds of a history of suicide attempt in a multiplicative fashion: an overwhelming 97 % of BD-I who had both comorbid drug and alcohol-use disorders had made at least one suicide attempt (Sublette et al. 2009). Contrarily, a recent study using data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) failed to demonstrate such an additive effect of drug use disorders on suicidal behavior in BD patients who also have alcohol-use disorders (Oquendo et al. 2010).

Sublette et al. pointed out three variables that were shown to mediate the increased risk for suicide attempt in this population, namely, traits of aggression, impulsivity, and hostility. The authors suggest these traits arise from the interaction of BD and substance abuse. Since the temporal relationships between the affective manifestations of BD, substance abuse, and suicide attempt are not yet clear, further prospective studies are suggested by them to elucidate the exact role of these traits as mediators of suicide attempt (Sublette et al. 2009). The implication of these traits in suicidality is not solely restricted to BP patients; in adult alcohol-dependent patients, a strong association between impulsivity and severity of depressive symptoms has been demonstrated (Jakubczyk et al. 2012). A recent model describing the constructs of behavioral disinhibition, associated with self-injurious behavior in adolescents, ascribed personality traits such as impulsivity and sensation seeking as key structural elements (Bogg and Finn 2010). A recent study using a large sample of adolescent self-reported questionnaires found significant associations between sensation seeking behavior and depressive symptoms or the occurrence of substance use problems. Students with high sensation-seeking behaviors were three times more likely to have symptoms of depression or substance abuse than students with low sensation-seeking behavior (Ortin et al. 2012). They also had a significantly higher risk for endorsing serious suicidal ideation or for having engaged in a suicide attempt, even after controlling for either depression or substance abuse (Ortin et al. 2012).

135.2.5 Gender Differences in Suicidality

The risk for suicidal behavior does not exhibit gender equality. This likely stems from multiple psychological, biological, and social between-gender distinctions that bear a dissimilar effect on mental states and behaviors associated with suicidal behavior. Trying to evaluate the moderating effect of gender on the SUD-suicidality

connection is fraught with methodological challenges since gender is differentially associated with suicidality, depression, and substance use. For instance, female adolescents are more likely to be depressed; among American youth aged 12–17, females were more likely than males to have past year MDE (12.1 % vs. 4.5 %) or MDE with severe impairment (8.3 % vs. 3.2 %) (NSDUH 2012b). Males, on the other hand, are more likely to use drugs and alcohol. On average, boys report cannabis use to a larger extent than girls do (19 % vs. 14 % in Europe and 25.9 % vs. 20.1 % in the USA) (Eaton et al. 2012; Hibell et al. 2012), although Rey et al. reported no such gender difference for Australian youth (Rey et al. 2002). Adolescent males drink more alcohol and report more frequent heavy episodic drinking (Eaton et al. 2012); additionally, females are more sensitive to alcohol-induced effects due to biological factors.

Regarding suicidality, females are more likely to have suicidal ideation, to make suicidal plans, and to attempt suicide (Eaton et al. 2012), whereas males are more likely to complete suicide (Bridge et al. 2006). Interestingly, in a large study tracking completed adolescent suicide rates in Finland over a period of 40 years, a surprising differential gender-specific trend of suicide rates was found. Although male suicide rates displayed a steady decrease since 1989, the female trend displayed a concomitant steady increase (Lahti et al. 2011).

135.2.5.1 Lesbian-Gay-Bisexual Population

The Lesbian-Gay-Bisexual (LGB) adolescent population is gradually and increasingly being exposed to the public eye and to scientific studies. This population suffers from increased rates of environmental stress which may lead to social isolation and interfere with normal adolescent development (Frankowski 2004). In a recent study, one-third of adolescents aged 16–20 years met DSM-IV criteria for mental disorders and 15 % for major depression (Mustanski et al. 2010). Furthermore, LGB youth are more likely than their peers to have been victimized and threatened and to have been engaged in a variety of risk behaviors (Garofalo et al. 1998).

Although this is a "novel" population for health-related epidemiological research, relevant data can be generally drawn from large-scale adult population studies, in which sexual preference is more stable. These studies reveal increased risks for substance and alcohol dependence as well as for suicidality. A large meta-analysis concerning LGB suicidality and encompassing almost 12,000 nonheterosexual adults found the lifetime risk ratio for suicide attempts among LGBs to be 2.5 compared to the heterosexual population. The pooled data also revealed that alcohol and other substance dependence over 12 months was also 1.5 times higher among LGBs (King et al. 2008). Another large study including representative populations of LGB adults from the UK displayed similar results. Specifically, increased risks for drug dependence ($OR = 1.70$), alcohol dependence ($OR = 2.05$), lifetime suicidal thoughts ($OR = 1.85$), and suicide attempts ($OR = 2.21$) were found in LGBs as compared to heterosexuals (Chakraborty et al. 2011).

Assessing data regarding this subpopulation in the adolescent age group is not a simple task. Most LGB youth do not openly present themselves as such, and many

are not without doubt regarding their sexual preferences, a substantial part of them go on to change their sexual orientation throughout this transitional period (Needham 2012). This task is made even harder when trying to retrospectively assess whether same-gender sexual affiliation was present, requiring the differentiation of self-defined sexual orientation from practiced sexual relationships which may or may not be in accordance with the sexual affiliation.

Among high school youth in the USA, 1.3 % of students identify themselves as gay or lesbian and 3.7 % as bisexual (Kann et al. 2011). Another 4.7 % of students present themselves as "unsure of their sexual identity," yet it is unknown whether this large group shares similar behavioral attributes as the LGB group or not.

Sexual minority students are more likely to engage in health-risk behaviors than other students (Garofalo et al. 1998). They display higher prevalence of binge drinking and report a higher rate of current marijuana use (Kann et al. 2011). A meta-analysis exploring the connection between nonheterosexual sex orientation and substance abuse found an increased risk for SUD among LGBs, including lifetime use of alcohol ($OR = 2.23$) and marijuana ($OR = 2.58$) (Marshal et al. 2008). Data from the latest YRBS report the prevalence of students having attempted suicide to be 6.4 %, 25.8 %, and 28 % for heterosexual, gay/lesbian, or bisexual students, respectively (Kann et al. 2011). Gay/lesbian students were almost six times more prone to commit a suicide attempt that resulted in an injury, poisoning, or an overdose that had to be treated by a doctor or nurse (Kann et al. 2011). Data gathered from a national longitudinal study of adolescent health in the USA revealed that LGB adolescents reported higher rates of suicidal ideation and suicide attempts than did non-LGB adolescents, even after controlling for race, gender, and age (Silenzio et al. 2007). Most importantly, risk factor analyses exposed different patterns of suicide related risk factors between LGB and non-LGB adolescents; problematic drug use was more strongly associated with suicidal ideation among non-LGB adolescents, as was the association between depression and suicide attempts (Silenzio et al. 2007). The authors suggest that different treatment targets should be sought for this population following the elucidation of specific suicidal risk factors relevant to LGB adolescents. A recent meta-analytic review comparing suicidality and depressive symptoms in sexual minority and heterosexual youth found increased suicidal behavior ($OR = 2.9$) and depressive symptoms in this sexual minority population (Marshal et al. 2011). Of note in this analysis was the description of an increase in the level of disparity between both populations as the severity of suicidal behavior increased ($OR = 1.96$, 2.2, 3.18, 4.17 for suicidal ideation, intent, attempt, serious attempt requiring medical attention accordingly) (Marshal et al. 2011), stressing the need for health-care personnel to pay heightened attention to suicidal behavior when encountered in LGB youth and when performing a suicide risk assessment.

Prospective studies are in demand to promote the identification of distinct attributes concerned with suicidality in this population through their transition into adulthood and maturation of sexual preference. In a large longitudinal study following a cohort of over 1,000 children from birth to age 21, the sexual orientation was studied at age 21 retrospectively from age 16 to 21. The correlation

analyses between sexual orientation and suicidality revealed a fivefold risk for such behavior in LGBs through the cohort period. The risk for LGB substance dependence was almost double, although not statistically significant ($p = 0.086$) (Fergusson et al. 1999). The prospective nature of this study allowed for the evaluation of social and familial backgrounds of the subjects, and indeed some differences were found between LGBs and other cohort members in their familial background suggesting a more troubled childhood for LGBs. Interestingly, controlling for these differences in the statistical analyses had a negligible effect on the unadjusted results and thus might reflect a need to focus on developmental and behavioral factors instead.

135.2.6 Age Differences in Suicidality

Zalsman has speculated that the timing of onset of gene-environment interactions leading to adolescent suicidality is crucial. He postulates that specific brain-development time windows may be critical for this interplay to emerge as behavioral phenotypes (Zalsman 2010, 2012). Clinical observations of age influences on suicidal behavior are evident and the risk for suicidal behavior has been shown to increase through the transition from childhood to adolescence in such a way that late adolescents (generally defined as over 15 year old) exhibit increased risks for suicidal attempts and completion as compared to early adolescents (Dervic et al. 2008; Waldrop et al. 2007; Windfuhr et al. 2008). Indeed, in early adolescence suicide is the tenth cause of mortality worldwide and at age 15–19 years there is a dramatic leap to second place (Patton et al. 2009). In older adolescents the perception of risk from using alcohol and marijuana is lower (NSDUH 2013) and the use of drugs and alcohol as well as practicing binge drinking is increased (NSDUH 2012a). For instance, in a study by Rey et al., the lifetime use of cannabis tripled between ages 13 and 15 years and a further increase of about 60 % occurred between 15 and 17 years (Rey et al. 2002). Furthermore, late adolescents' suicidal behavior is more associated with increased alcohol and drug use (Brent et al. 1999; Hysinger et al. 2011; Singh and Lathrop 2008) even though cannabis use (Fergusson et al. 2002) or heavy episodic drinking (Aseltine et al. 2009) may have a more prominent effect on suicidal behavior in school-aged children as compared to older adolescent users. These data clearly strengthen the notion that public-health leaders should prioritize their efforts toward younger school-aged adolescents.

135.2.7 Future Studies

Whereas the epidemiological and clinical data linking substance abuse to suicidality are compelling, basic science research encounters many difficulties in establishing this connection. Several problems arise to hamper the fundamental demand to minimize heterogeneity in the studied variables. First, there is no consensus as to the exact age span of adolescence although it is traditionally

regarded as the time period between ages 10 and 25 years. Furthermore, this time length encompasses developmental stages such as puberty and postpuberty, associated with dramatic hormonal and physiological changes (e.g., the menarch) which cannot be constrained by strict temporal limits. Second, adolescence is a period of a dramatic psychosocial transition from childhood to adulthood, and this change is anatomically supported by a profound increase in brain plasticity (Casey et al. 2008) including rostrocaudal white matter increase (myelinization) and accelerated dendritic pruning (Giedd et al. 1999) leaving few brain regions and neurochemical pathways unchanged. Suicidal behavior or even thoughts might turn out to variably modify brain activity and plasticity in a similar way as does substance abuse (Churchwell et al. 2010) or depression (Tao et al. 2012). Trying to account for this variability in brain connectivity in time and space over at least a 10-year period seems presently impractical. Third, for obvious reasons, studying human brain morphology and activity, particularly those of children and adolescents, should be undertaken by employing noninvasive means. These means are presently scarce and thus most studies rely on comparative neuroimaging techniques alone.

These methodological challenges are demonstrated in a comprehensive overview of the relationship between alcohol and suicide by Pompili et al. (2010). They describe this causal relationship as being inconclusive and highly suggestible at best in light of the many neurotransmitter systems which are affected by ethanol, with varying spatial and temporal modifications regarding target brain regions.

Nevertheless, in the molecular level, a substantial volume of research has been accumulated relating to neurobiological changes associated with suicidality in adolescents. While these studies present convincing data regarding a genetic predisposition to suicidality (Zalsman 2012) as well as altered receptor and signal transduction pathways associated with suicidality (Pandey and Dwivedi 2012), they seldom address the role of substance abuse as a modifier to these neurobiological changes.

Suicidality is undoubtedly a complex behavioral phenotype. Currently, researchers studying the heritability of suicidal behavior are increasingly concerned with endophenotypes of suicidal behavior (Mann et al. 2009) and less so with single genes, although in distinct cases a direct connection can be drawn between single genes and suicide-related features such as impulsivity (Bevilacqua et al. 2010). An important workshop convened for the purpose of the identification of candidate biological and clinical endophenotypes associated with suicidality found the most promising endophenotypes to be aggression/impulsivity trait, early onset major depression, neurocognitive function, and cortisol social stress response (Mann et al. 2009). Most recently specific endophenotypes for drug dependence have also been described (Ersche et al. 2012b) which may be associated with a heritable familial vulnerability to drug dependence (Ersche et al. 2012a). Other studies highlight the role of inherited alterations in regulatory mechanisms of the hypothalamic-pituitary-adrenal (HPA) axis in the development of alcoholism (Sher 2006). It is also suggested that aberrant glucocorticoid modulation of

raphe-hippocampal connections in alcohol consuming adolescents may contribute to the emergence of suicidal behavior (Sher 2007).

It will be interesting to explore how relevant are these newly defined endophenotypes to the adolescent age group and to what extent do they overlap in specific individuals. This might pave the path for early targeted detection of high-risk suicidal patients and enable the utilization of individualized biological-based suicide prevention schemes.

135.2.8 Treatment and Prevention

How effective are drug prevention programs? An optimistic report comes from the Office of Applied Studies, a branch of the Substance Abuse and Mental Health Services Administration (SAMHSA). This report examined age-related developmental increases in rates of substance use among different cohorts of American youths aged 12–17 from year 2002 to 2008. It also compared overall levels of use across different cohorts. As expected, the lifetime prevalence of use of alcohol and marijuana within a cohort increased with rising age. But although in all of the cohorts the prevalence rate by the age of 17 year was more than 60 % for alcohol and over 30 % for marijuana, logistic regression model results showed that adolescents in later cohorts (e.g., those aged 17 in 2008) were significantly less likely to use these substances compared with youths in earlier cohorts (e.g., those aged 17 in 2002 (SAMHSA 2013)). The lower rates of lifetime use of alcohol and marijuana in later cohorts of youths compared with earlier cohorts provide encouraging news for professionals working in substance abuse prevention. This is relevant to global initiatives as well since the decrease in substance use prevalence may be a global- rather than local-scale trend. Data from a recent Australian study encompassing approximately 20,000 school-aged adolescents has shown that the proportion of students reporting past-year cannabis use has halved from 32 % in 1996 to 14 % in 2005 (Roxburgh et al. 2010). Other reports from several European countries display a similar trend although with a less dramatic decrease in cannabis use prevalence (−10 % between 1999 and 2009) (Molinaro et al. 2011).

Despite this reassuring trend in substance use prevalence in the last decade, youth perception of drug prevention efforts is not encouraging. Between the early 2000s and 2011, the percentages of adolescents reporting recent exposure to drug or alcohol-use prevention messages through media and school sources remained relatively stable or displayed a modest decline (NSDUH 2013). Also, in 2011, 40 % of adolescents reported that they did not talk with their parents about the dangers of substance use, and 25 % did not receive prevention messages through media or school sources (NSDUH 2013). In a study spanning several sociodemographic groups in the USA of the attitudes and beliefs about adolescent suicide held by adolescents and their parents, both identified adolescent suicide as a major problem but did not recognize it as a problem in their own community (Schwartz et al. 2010).

Efforts should also be directed to improve available treatment options since data from recent US surveys display dismal reports of severe undertreatment of adolescent illicit drug and alcohol-use problems particularly in specialized centers. A national survey of American adolescents aged 12–17 conducted in 2011 reported that 1.2 million adolescent were in need for treatment for an illicit drug use problem and 978,000 youths needed treatment for an alcohol-use problem. Of these, only 125,000 (10.5 %) received treatment for drug abuse and only 63,000 (6.4 %) for alcohol abuse at a specialty facility (NSDUH 2012a). These statistics are presumed to be even worse in many other countries due to stigma, underdiagnosis, and shortage of relevant clinical facilities.

The Cannabis Youth Treatment (CYT) study, which is the largest psychosocial outpatient treatment trial to date completed in adolescents with SUD (Dennis et al. 2002), compared five promising treatment strategies. The study found that in terms of efficacy and cost-effectiveness, the use of five sessions of Motivational Enhancement Therapy plus Cognitive Behavioral Therapy (MET/CBT5) is the most promising regimen under randomized field trial conditions in treating SUD, at least as an initial treatment effort (Dennis et al. 2004). Translating this evidence-based therapy into community-based settings is not a simple task (Riley et al. 2008), but may very well prove to be effective (Ramchand et al. 2011). For a comprehensive review of further substance abuse-related treatment and prevention strategies, see Toumbourou et al. (2007). However, the CYT as well as other SUD-treatment studies do not provide an answer to the question whether SUD-targeted treatments have a suicide-lowering effect at all. Although some reports imply that this may be true for youth with comorbid depression (Emslie et al. 2010; Goldstein et al. 2009), addressing this question demands a prospective study sufficiently powered to capture these relatively infrequent events.

Suicide prevention programs and treatment strategies are also abundant, and a multidimensional approach is generally encouraged although hard to be implemented using evidence-based approaches (Mann et al. 2005). A major challenge to be overcome for the successful implementation of prevention and treatment strategies stems from the fact that most suicidal adolescents do not reach for help prior to their suicidal acts. Only 14 % of young people in the UK who completed suicide were in contact with mental health services in the year prior to their death, incidentally, 71 % of these reported concomitant substance abuse (Windfuhr et al. 2008). Also, in a case-control study on the utilization of health-care services among Canadian adolescents aged 11–18 years prior to completed suicide, Renaud et al. described that although 95 % of suicide completers suffered from mental disorders, over two-thirds of them had no treatment contact within the month prior to the act, while only 12.7 % were in contact with psychiatric services during that same period (Renaud et al. 2009). Psychoeducational suicide prevention programs have generally shown to positively affect knowledge and certain attitudes concerning suicide (Kalafat and Elias 1994; Portzky and van 2006) although a paucity of large-scale controlled trials limits a clear-cut conclusion regarding their efficacy. Other prevention strategies such as

screening efforts, gatekeepers training, means restriction, and others have also been described (Bursztein and Apter 2009), and their usefulness reviewed elsewhere (Hawton et al. 2012).

The exposure of youth to various suicidal behaviors through the media (newspapers, television, and Internet) may carry a substantial impact on suicidality prevalence which should not be underestimated (Dunlop et al. 2011; Gould and Shaffer 1986; Niederkrotenthaler et al. 2010; Shoval et al. 2005). Despite that, media sources and particularly Internet sites may also lend real-time, confidential, and easy-to-access sources for suicidality counseling and support and provide an accessible route for treatment referral.

135.3 Conclusion

Although the act of completed suicide is extremely hard to predict, many risk factors have been well established and studied. Efforts to further maximize the accurate assessment of high-risk individuals based on these should be encouraged. Reducing suicide attempts in these individuals remains a challenge since it is not yet clear to what extent eliminating the associated risk factors will in effect result in the reduction of the risk for suicidal behaviors. In this context, efforts to strengthen anti-suicidal resiliency (Borowsky et al. 2001; Forman and Kalafat 1998) through local or national initiatives (McNamara 2013) have gathered interest, although their effectiveness remains to be proven.

It is apparent that both suicidality and SUD are highly prevalent in the young population and that both carry an increased risk for morbidity and mortality, increasing with older age. The counter-effect of these two complex behavioral states on each other increases the risk for suicidal behavior in adolescents with SUD as opposed to those without. This may largely be due to the fact that both are associated with decreased inhibition and increased impulsivity that lead to impaired decision making manifested in risk-taking and reckless behaviors. In the proximal time scale, co-occurring SUD may facilitate the transition of ideation to action, whereas in the distal time scale, it may contribute to increased stress by adversely affecting the adolescent's environment and circumstances (Esposito-Smythers and Spirito 2004).

The ongoing efforts of large-scale initiatives that monitor teenage substance use trends and suicidality should also be supported. Relevant data gathered from these facilitate the analysis of global as well as local trends in substance use and their correlation with suicidality. Future clinical studies should follow these changes in temporal trends to provide rapid and relevant reports of the usefulness of prevention efforts utilized. To date, available treatment options only partially rely on evidenced-based knowledge due to a lack of studies on the one hand and methodological difficulties on the other. Carefully planned large-scale prospective studies are in need to provide a stronger evidence base for assessing clinical benefits of prevention and treatment plans. A major goal for basic science research remains to locate a low-cost, minimally invasive, and highly specific endophenotype marker

for suicide. Such a marker may be more pronounced or relevant in adolescents with SUD due to the strong association between the two phenomena.

The prevention of suicide in youth and children has become one of the most challenging goals of health systems worldwide. In defined high-risk populations such as the LGBs, efforts for early detection must be increased by the health system, and careful evaluation of suicidality should be made based on validated assessment scales and established risk factors while avoiding stigmatization. Wide gaps appear between therapeutic strategies in different countries and even within countries. This may reflect the paucity of evidence-based proven efficacy of current therapies targeted either for SUD or suicidality. The association between SUD and adolescent suicidality is highly influenced by other psychiatric comorbidities, primarily but not exclusively mood disorders, which are most prevalent among these patients and confer an increased risk for additional psychopathology and completed suicide. SUD patients with suicidal behaviors are increasingly diagnosed as suffering from "dual diagnosis" without a concomitant referral to specialized treatment facilities. Regretfully, in most countries, the therapy for SUD is not part of the "mainstream" psychiatric health system, and this artificial dichotomy most probably hampers the integrative treatment effort which suicidal adolescents and their families require. We propose that for these patients, a holistic treatment approach is needed to be implemented in specialty facilities. SUD as well as other psychiatric comorbidities and emergent suicidal behaviors should be addressed concurrently because a mutual effective connection between these conditions, although not yet well understood, is most evident.

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Risk and Protective Factors for Substance Use and Abuse

136

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Contents

Abstract

This chapter presents an overview of international research into the risk and protective factors, developmental course, and long-term consequences of adolescent substance use within a contextual developmental framework informed by Family Interactional Theory (FIT). According to this theory, adolescent substance use is best understood as determined by a multitude of risk factors in different developmental contexts (i.e., individual, micro- and macro-contextual).

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The chapter also describes how the developmental pathways to adolescent substance use can be modified by protective factors, which have the ability to mitigate the impact of risk factors on adolescent substance use and abuse. FIT focuses on the role the parent-adolescent relationship, especially a non-conflictual mutual attachment relationship, plays in insulating children and adolescents against risk factors for substance use and abuse. The chapter also presents approaches to the prevention of adolescent substance use. In addition, the chapter emphasizes the importance of relevant and appropriate cultural and developmental factors in prevention. Directions for future research are presented.

136.1 Introduction

In the following, we present an overview of the etiology, developmental course, and long-term consequences of adolescent substance use within a contextual developmental framework (Brook et al. 1990). Our research and that of others indicate that adolescent substance use is a complex phenomenon that is best understood as determined by a multitude of factors at different levels of development (i.e., individual, micro- and macro-contextual; e.g., Bronfenbrenner 1979). In addition, some of the precursors of adolescent drug use may be mitigated by later events and circumstances. These developmental pathways and mechanisms are reflected in Family Interactional Theory (see below), a developmental framework for understanding some of the determinants of substance use and abuse.

136.1.1 Theoretical Orientation

Several theories (e.g., FIT, Brook et al. 1990; Fagan and Hawkins 2013; Farrington and Loeber 2013) emphasize the importance of examining multiple predictors of deviance and highlight the significance of viewing substance use from a developmental perspective. For instance, individual risk factors and risk factors in the family setting such as a distant parent-child attachment relation and low monitoring are especially significant in the early years (Moffit 1993). At a later stage of development, in late childhood and adolescence, the peer group and school take on added significance. During middle and late adolescence, community factors play a greater role (Farrington 2003). Consequently, as noted by Brook and colleagues (2006d) and Fagan et al. (2011), the factors that lead to drug use may differ depending on the individual's stage of development. Finally, some risk factors such as the family bond and ego integration are of significance at each of the stages of development.

As noted by Fagan and Hawkins (2013), the most significant targets for intervention include risk factors and protective factors noted in theories of criminology and substance use (Fagan and Hawkins 2013) and found in longitudinal studies of substance use (Farrington and Loeber 2013).

Family Interactional Theory (Brook et al. 1990) is a multidimensional conceptual model, which postulates that the development of substance use over time is best explained by a sequence of influences from multiple individual-level and contextual domains. The primary developmental context is the family of origin, including parental personal attributes and attitudes (e.g., psychopathology), parental behaviors (e.g., substance use), parental child-rearing behaviors, and the quality of the parent-child relationship as well as the quality of the marital relationship. The familial context helps shape the most proximal influence on adolescent substance use, namely, the adolescent's personal attributes, including personality, attitudes, and behaviors. Personal attributes, in turn, influence the adolescent's choice of peer affiliations. Both personal attributes and peer affiliations are directly related to substance use. Adolescents who have personalities characterized by emotional under-control, who endorse more unconventional attitudes, and who experience high levels of affective distress are more likely to use drugs, as are adolescents who affiliate with deviant peers.

The cornerstone of FIT, which incorporates elements of attachment theory and social learning theory, is the parent-child mutual attachment relationship, as it operates at the center of other psychosocial domains which are related to adolescents' substance use. Attachment mediates other familial and contextual dimensions and serves as a major buffer for risk conditions. FIT also describes intervening mechanisms, which can modify the relationships between risk and protective factors and substance use. Thus, FIT describes the major pathways to substance use from childhood to adulthood and explains variations in these pathways. Finally, FIT focuses on the interaction of risk and protective factors as noted below.

136.1.2 Interaction of Risk and Protective Factors

Risk factors include factors that are antecedent or concomitant to substance use and increase the probability of adolescent substance use. Such risk factors include attributes of the individual, family, peer group, school, and community. Protective factors, on the other hand, reduce the risk of adolescent substance use and abuse. Protective factors exist at the community level (e.g., community rewards for prosocial involvement), family level (e.g., family attachments), school level (e.g., school rewards for prosocial involvement) (Briney et al. 2012; Brook et al. 2008), and personality level (e.g., ego integration). Besides having a linear negative relationship with substance use, protective factors can also offset risk factors or enhance other protective factors. In the first type of interaction (risk/protective), risks are attenuated by protective factors by buffering individuals against the pathogenic influences of risk factors. For example, among ethnic and racial minority youth, having a strong ethnic identity may mitigate the influence of risk factors for substance use (e.g., from substance-using peers) (Pahl and Brook 2004). The second type of interaction (protective/protective) is a synergistic process, in which one protective factor strengthens another, so that the combined effect of both protective factors is greater than their sum.

136.1.3 Developmental Course of Substance Use

Research conducted in the past decade has identified developmental patterns of substance use in the form of differential longitudinal trajectories from adolescence into adulthood using such methods as growth mixture modeling and cluster analysis (e.g., Brook et al. 2006a; Chassin et al. 2008; Costello et al. 2008; Flory et al. 2004; King and Chassin 2007; Orlando et al. 2004; Schulenberg et al. 2005; Windle and Wiesner 2004). These studies have found different classes of substance users characterized by different rates and levels of substance use over time. Varying by substance (i.e., tobacco, alcohol, marijuana), research has identified between three and six different trajectories of substance use. For example, studies of tobacco use typically find a group of low or nonusers, an early-starting group of continuous heavy smokers, and a group of quitters (e.g., Chassin et al. 2008; Orlando et al. 2004). Some also find late starters (e.g., Brook et al. 2006b) and/or increasers (e.g., Pahl et al. 2011). Trajectories of substance use can be used to predict long-term outcomes and thus provide information about the consequences of specific developmental patterns of use over time (e.g., of early-onset heavy use versus moderate use).

Recent work has also identified trajectories of the co-occurrence of tobacco and marijuana use and psychological outcomes (e.g., Brook et al. 2012a). Other papers have looked at the co-occurrence of substance use with psychological symptoms (e.g., Otten et al. 2010; Pahl et al. 2013) and other adverse outcomes (e.g., victimization; Pahl et al. 2013). These studies have the advantage of mapping the occurrence of use of two or more substances and/or other outcomes over time, thus highlighting patterns of dual and polysubstance use and the joint developmental patterns of substance use with other risk outcomes. These studies can identify groups of high-risk individuals and help predict membership in such a group from earlier risk factors, which provides important information for both prevention and treatment.

Research supports the stability of substance use from adolescence to young adulthood. Stability in substance use has been documented for alcohol use (Flory et al. 2004), tobacco use (Palmer et al. 2009), and the use of illegal drugs (Bachman et al. 1984). Several researchers (Brook et al. 2007; Flory et al. 2004; Roche et al. 2008) have found that early-onset substance use is highly related to later substance abuse (Brook et al. 2007; Flory et al. 2004). Jenkins and colleagues (2011) reported that early-onset alcohol use is correlated with vulnerability to later alcohol abuse as well as dependence. Nevertheless, it is important to note that adolescents who use drugs do not necessarily become addicted to drugs (Frisher et al. 2007). There is also evidence that adolescents who use legal drugs are more likely to use marijuana at a later point in time, as well as become dependent on illegal drugs (Brook et al. 1999, 2007). For example, Lessem et al. (2006) reported that adolescent marijuana use is associated with the use of other illegal drugs at a later point in time. Studies conducted internationally have also found that adolescents' use of legal drugs generally precedes the use of illegal drugs (e.g., Patrick et al. 2009). Agrawal et al. (2013) also report that tobacco use often precedes the use of other substances.

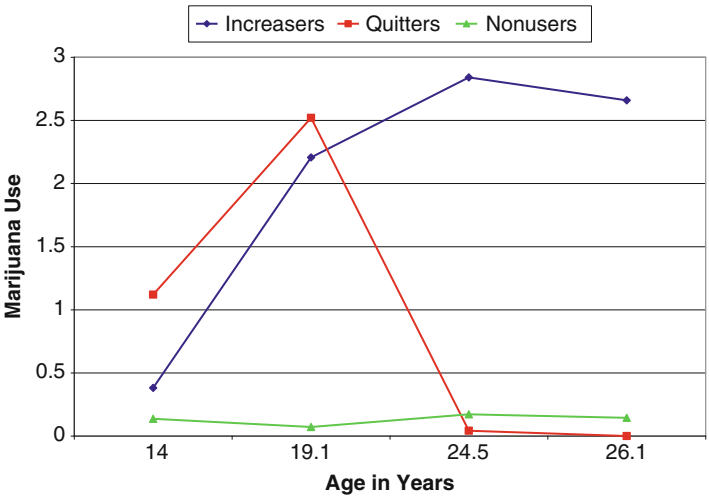

Fig. 136.1 Trajectories of Marijuana Use for African American and Puerto Rican Women (N=474)

136.1.4 Consequences of Substance Use and Abuse

Substance abuse in adolescence is a serious health concern as it is related to underachievement at school, delinquency, adolescent pregnancy, sexually transmitted diseases, psychiatric morbidity, physical health conditions, and dysfunction in the family (Greenblatt and Gfroerer 1994). The harm to society as a consequence of adolescent substance abuse includes costs related to the criminal justice system and increased costs of health care. There is also ample evidence from international studies that the use of substances is related to these adverse outcomes (e.g., Pluddemann et al. 2008) and to violence and unintentional and intentional injuries (e.g., Peltzer and Pengpid 2012; Rudatsikira et al. 2007). The use of substances during adolescence is also associated with poorer educational attainment, in terms of the completion of a degree or college attendance in young adulthood (King et al. 2006).

In a recent longitudinal study, Pahl et al. (2011) examined the developmental patterns of marijuana use and their relationship with subsequent psychological adjustment in a community-based sample of urban African-American and Puerto Rican women. They identified three trajectories of marijuana use among these females (see Fig. 136.1).

The findings the indicated that high-frequency marijuana use over time among females was related to greater psychopathology as reflected in higher scores on indicators of psychological maladjustment (e.g., anxiety, depression). Marijuana use should thus be considered a risk factor for the development of psychological distress. In treating marijuana users with such a pattern of long-term, high-frequency use, practitioners should be aware of the adverse effects on

psychological adjustment. Similarly, prevention programs should focus on the long-term psychological cost associated with marijuana use, noting that the best psychological health is reported by those who abstain from the drug.

136.2 Summary of Risk Factors for Substance Use

136.2.1 Demographic Risk Factors for Adolescent Substance Use

136.2.1.1 Male Gender

Gender differences in substances use are evident in legal and illegal drug use (Johnston et al. 2012a). In the United States, adolescent males tend to report greater use of alcohol and illicit drugs, particularly frequent use (Johnston et al. 2012a). For example, males report higher rates of heavy drinking. Among US teens, tobacco use is approximately equal between boys and girls though boys tend to smoke more than girls as they get older. For example, in 2012, among 12th-graders, the 30-day prevalence of tobacco use was 19 % for males and 14.5 % for females (Johnston et al. 2012b).

Gender differences in substance use vary by country and cultural subgroups, depending on the prevalent cultural and gender norms. For example, in South Africa, males smoke more than females. This gender difference is particularly strong among Black adolescents. There are strong cultural taboos against smoking for South African women (Steyn et al. 2002), which seem to result in lower levels of cigarette use (Marks et al. 2001; Steyn et al. 2002).

136.2.1.2 Low Parental Income/Socioeconomic Status (SES) and Education

Some recent research has found that adolescents from higher socioeconomic groups may be more likely to engage in drug use during early adulthood, although these results were not true for all ethnic groups or for the use of all drugs (e.g., Humensky 2010; Ritterman et al. 2009). In a longitudinal study conducted among adolescents in Mexico, Bojorquez et al. (2010) found that the father's lower level of education was associated with more drug use initiation. In another study conducted in Mexico, Ritterman et al. (2009) found that higher SES adolescents were more likely to report tobacco and alcohol use, but no more likely to report illicit drug use. The increased disposable income that permits easier access to drugs is often cited as a reason for these findings. Indeed, Hanson and Chen (2007) found that higher financial resources were more strongly associated with substance use than social status.

136.2.1.3 Parental Divorce and Single Parenthood

The literature regarding parental marital status and substance use is somewhat inconsistent. Hope et al. (1998) reported that there was a weak relationship between parental divorce and substance use. In a prospective study of a birth cohort followed up until the age of 21, Hayatbakhsh et al. (2006) reported that children whose mothers changed their marital status were more likely to have used marijuana (or have a cannabis use disorder) than those whose mothers' marital status was

stable. When examining the effect of marital status on children, it is important to take into account a number of factors such as the mothers' and fathers' relationships with their offspring, the age when the separation occurred, relations with other family members, and so on. Clearly, further research is needed to gain an understanding of the effect of marital status on the offspring's substance use.

Single parenthood has also been examined as a predictor of adolescent substance use, with the results varying by parental gender (Eitle 2006). Some studies suggest that adolescents who are raised only by a mother may be more likely to engage in drug use due to reduced socioeconomic resources and less monitoring (Amato 2000; McLanahan and Sandefur 1994). However, one study found that the risks for alcohol use are higher for children living only with a father (Eitle 2006). The results for the use of other drugs and those pertaining to different ethnic groups were inconsistent (Eitle 2006).

Another family structure that is more common in low- and middle-income countries is the child-headed household, or situations where children live as orphans. Evidence is emerging to show that children who are orphaned, homeless or live on the streets without parental or adult supervision are at greater risk of using substances (Meghdadpour et al. 2012).

136.2.1.4 Adolescent Employment

During adolescence, the number of hours worked per week is related to substance use (McMorris and Uggen 2000). Schulenberg et al. (2005) reported that adolescents who worked l6 h or more per week were more likely to become chronic marijuana users. It has been argued that increased work is associated with increased stress and peer associations that may increase adolescents' risk of drug involvement (Kaestner et al. 2013).

136.2.2 Personality and Psychopathology as Risk Factors for Adolescent Substance Use

136.2.2.1 Internalizing and Externalizing Behavior and Comorbidity with Substance Use Disorders

Investigators have identified two major pathways among individual predictors of addiction. The first pathway is through negative emotionality, sometimes referred to as internalizing psychopathology. The second pathway is through deviant or externalizing behavior (Krueger et al. 1998). According to Krueger et al. (1998), internalizing disorders include several disorders such as depression and anxiety. Externalizing disorders refer to antisocial behavior disorders [e.g., conduct disorder (CD), oppositional defiant disorder (ODD)]. There is also evidence of comorbidity or the co-occurrence of internalizing and externalizing disorders with SUDs. Results from the Dunedin Birth Cohort Study (Anderson et al. 1987) showed that over one quarter of the adolescents with SUDs also experienced depression. Research has also suggested that there is comorbidity between SUDs and anxiety among adolescents, with prevalence rates of about 7 % in the Children in the

Community Study (Brook et al. 1998; Cohen and Cohen 1996). Similar results emanate from research in various parts of the globe, including South Africa (Saban et al. 2010). In China, smoking was associated with depression and anxiety as well as with hostility among adolescents in a study involving 7th and 11th graders (Weiss et al. 2008).

Brook et al. (2006c) noted that individuals following a trajectory of early-starting continuous cigarette smoking were more likely than other individuals to be classified as having experienced internalizing problems during childhood. Several investigators have found that measures assessing aspects of externalizing behaviors are related to substance use, including tobacco use, marijuana use, and cocaine use. Such dimensions of externalizing behaviors related to substance use include unconventionality (Brook et al. 1999), delinquency (Morojele and Brook 2001), and antisocial or conduct problems (Bor et al. 2010).

Several types of drug use disorders are frequently comorbid with externalizing disorders. Chan et al. (2008) reported that over three-quarters of adolescents with a substance use disorder had at least one externalizing problem. Conduct disorder has been found to both co-occur with and predict SUDs (Brook et al. 2010; Elkins et al. 2007).

136.2.2.2 Comorbidity of Substance Use Disorders with Other Psychiatric Disorders

In a longitudinal study of co-occurring psychiatric disorders and substance use, Brook et al. (1998) reported that tobacco, alcohol, and marijuana use disorders predicted high rates of antisocial personality disorder in adulthood. ADHD has also been found to be comorbid with SUDs (Brook et al. 2010). In addition, research has found comorbidity of substance use disorders with post-traumatic stress disorder and major depressive disorder in adolescent populations (Kilpatrick et al. 2003).

There are several hypotheses regarding the comorbidity of disorders. First, comorbid disorders may share causal factors. It may be that common genetic influences account for the comorbidity between disorders of addiction and externalizing behaviors. Shared underlying psychosocial factors may also play a role in explaining the comorbidity of substance use and internalizing disorders. For example, comorbidity between substance use and depression may be due in part to impulsivity (Zilberman et al. 2007), low self-control (Otten et al. 2010; Pahl et al. 2013), or lack of social support (de Graaf et al. 2004).

Second, there may be a reciprocal relationship between substance use and other psychiatric disorders. For example, alcohol use may increase the likelihood of depression and depression may lead to greater alcohol use. Finally, according to the self-medication theory (Khantzian 2012), substance use is preceded by other psychiatric disorders.

It is most likely that the complex interplay of genetic predispositions and environmental influences ultimately leads to both substance use disorders and internalizing disorders. According to Tsuang and colleagues (2012), "[. . .] psychosocial and environmental factors interact with genetic predispositions toward internalizing and addictive pathology, influencing the neurobiology and neurochemistry

of affected individuals" (p. 152). Future longitudinal research should attempt to disentangle the mechanisms that operate between the addictive diseases and other forms of psychopathology.

136.2.2.3 Other Personal Risk Factors

Additional personal characteristics that are often associated with substance use among adolescents include various personality attributes such as low self-esteem and low religiosity. Although much research suggests that adolescents with lower self-esteem are more inclined to use substances, the association between self-esteem and substance use is complex and dependent on the substance of interest (e.g., Wild et al. 2004). Wild et al. (2004) found among Grade 8 and 11 students in a study in Cape Town, South Africa, that self-esteem within the family and school domains were particularly important. A study with adolescents in six countries across Europe found no significant association between self-esteem and substance use (Kokkevi et al. 2007).

The more involved in religious activities, the less likely adolescents are to use substances (e.g., Miller et al. 2000). Religiosity has also been found to be negatively associated with drunkenness among adolescents in a study conducted in Cape Town, South Africa (Parry et al. 2004). However, these effects are not consistently found and may be a function of factors such as ethnicity, as found in a study among adolescents in Russia (Pokhrel et al. 2011), or gender, as found in a study in Hungary (Piko and Fitzpatrick 2004). Other personality traits related to substance abuse include sensation seeking (Cloninger et al. 1988) and poor planning (Clark et al. 2005). Behavioral problems that predict drug use include physical aggression (Unger et al. 2003), bullying (Farrington et al. 2011), and early sexual involvement (Hallfors et al. 2002).

136.2.3 Familial and Peer Risk Factors for Adolescent Substance Use

136.2.3.1 Familial Substance Use

Familial substance use is another risk factor for adolescent substance use and abuse. In a longitudinal study about the effects of parental smoking, occupation, and education on offspring tobacco use in adulthood, Fagan et al. (2005) found that parental smoking, blue-collar occupational status, and low parental educational achievement were related to smoking among adult offspring. Findings imply that parental smoking is important to consider in the establishment of prevention and intervention programs. Results suggest that the parent-child bond serves to intervene between parental smoking, educational and occupational status, and offspring smoking (see Fig. 136.2).

In a series of papers, Chassin and colleagues (2002; King and Chassin 2007) reported that the offspring of alcoholics studied from childhood to young adulthood were far more likely to be binge drinkers or have an alcohol use disorder than those of nonalcoholics. Maternal substance use has also been found to be related to adolescent

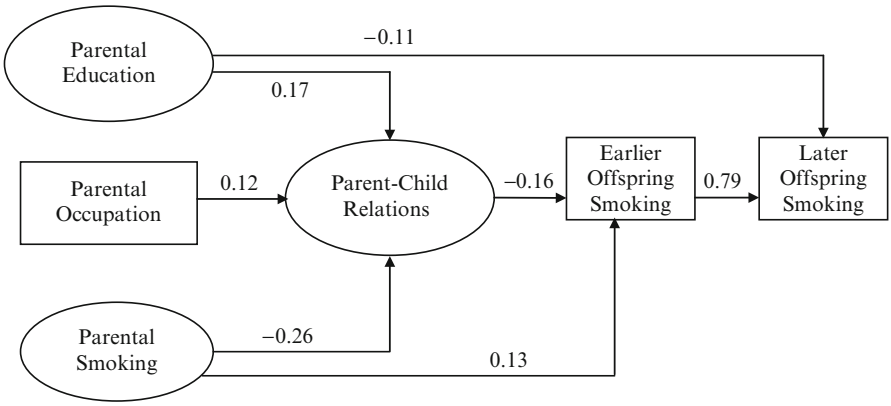

Fig. 136.2 Structural equation model predicting offspring smoking in late twenties (T5) from parental education, occupation, smoking, and child-rearing variables. All coefficients are statistically significant $p < .01$

substance use (Buu et al. 2009). A family history of substance misuse is also associated with increased adolescent alcohol consumption (Moore et al. 2010). When both parents use substances, there is an increased likelihood that the offspring will also use substances. Brook and colleagues (2006a) have emphasized the need to examine the mediators and moderators of the association between parental and adolescent substance use. For instance, Maalouf (2010) reported that parental substance use was associated with the parent-offspring relationship, which, in turn, was related to the offspring's substance use. There is also evidence that siblings play an important role in the adolescents' drug use (Boyle et al. 2001; Brook 1991).

136.2.3.2 Family Relations

Family conflict, whether between the parent and partner or parent and offspring, is related to adolescent substance use (Madu and Matla 2003; Caballero et al. 2010; Madruga et al. 2012) and dependence on alcohol and drugs (Chen et al. 2005; Morojele and Brook 2001; Zhou et al. 2006). In terms of protective factors, four dimensions of parenting practices have been identified as important in lessening the risk of adolescent substance use: (1) a close mutual attachment relationship between parent and child, (2) parent-child communication, (3) parental monitoring, and (4) effective role modeling. A warm, close mutual parent-child attachment relationship insulates the child and adolescent from drug use (Brook et al. 1990). It is important to establish a close parent-child mutual attachment relationship early on in order to reduce the risk of substance use in the offspring (Brook et al. 2009). Lack of family support or bonding has been found to predict legal and illegal drug use (Brook et al. 1990; King and Chassin 2004). Family support also moderates the relationship between adolescents' personality attributes and their substance use (Engels and Willemsen 2004).

Parental monitoring is also important, as it enables the parent to supervise the child's behavior more generally and his/her drug use more specifically.

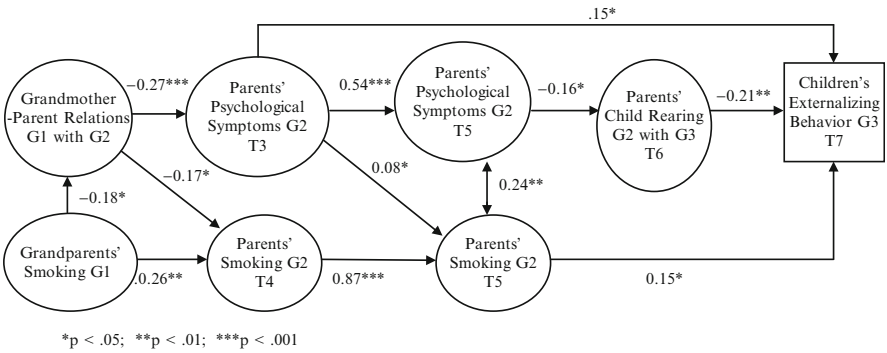

Fig. 136.3 Transgenerational transmission of risk factors for externalizing behavior. Structural equation model: standardized pathways (z statistic) to children's externalizing behaviors ($N = 230$). *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. T = Time

For instance, parental monitoring was related to a decreased risk of alcohol dependence (Guo et al. 2001) and of tobacco and alcohol use (Amoateng et al. 2006). Parental role modeling in the context of a close parent-child attachment is also critical for children's health behaviors. If the parent abstains from drug use and the adolescent identifies with the parent, the adolescent is less likely to use drugs.

The risks associated with parental substance use can also be transmitted across generations (Brook et al. 2012c). Based on Family Interactional Theory (FIT), Brook and colleagues (2012b) conducted a longitudinal study and examined the grandmother's (G1) relationship with her child (G2) and the association between the grandparents' smoking and the grandchild's (G3; mean age 11 years) externalizing behavior (see Fig. 136.3). The findings showed that a weaker G1-G2 attachment relationship and the grandparents' smoking were linked with externalizing behavior in the G3 child via G2 psychological symptoms (e.g., depression and anxiety), G2 smoking, and G2-G3 child-rearing practices.

136.2.3.3 Peer Risks

Peer substance use and peer encouragement of substance use are consistently the strongest predictors of adolescent substance use in all ethnic groups (Brook et al. 1990; Hussong 2002; Kandel 1996). Some research has found that the degree to which peers' substance use influences adolescents' own substance use varies by ethnicity. Unger and colleagues (2001), for example, found that the influence of friends' smoking on adolescents' smoking was stronger among White adolescents than among Pacific Islanders, African Americans, and Latinos.

The relationship between peers' substance use and that of adolescents themselves is reciprocal. On the one hand, adolescents' substance use may be influenced by that of their friends. On the other, adolescent drug users are more likely to choose friends who use drugs as well (assortative peer selection; Kandel 1996). Peer norms favoring drug use are also of importance. If adolescents think that the majority of adolescents their age use drugs, they are more likely to use

drugs. Consequently, drug prevention efforts can use this "perception bias" by providing adolescents with valid information about the number of adolescents who use drugs. More generally, associating with deviant and delinquent peers is a risk factor for adolescent substance use (Fergusson et al. 2002).

136.2.4 Environmental Risk Factors for Adolescent Substance Use

136.2.4.1 Exposure to Violence and Trauma

Another important risk factor for adolescent substance use is exposure to violence and trauma, including contextual violence (e.g., Brook et al. 2003a), violent victimization (e.g., Boynton-Jarrett et al. 2008), and childhood maltreatment and/or sexual abuse (e.g., Anda et al. 2006; Fergusson et al. 2013). Violent victimization is frequently associated with substance use and abuse (Boynton-Jarrett et al. 2008; Kilpatrick et al. 2000; Schneider et al. 2011). Fergusson et al. (2002) found that sexual abuse during childhood was associated with dependence on alcohol and illicit drugs. People who have been victimized may use drugs to ameliorate the painful psychological consequences of victimization, and in part, to self-medicate symptoms of post-traumatic stress disorder (Anda et al. 2006; Boynton-Jarrett et al. 2008).

136.2.4.2 Neighborhood Risks

Neighborhood factors influence adolescent substance use both directly and indirectly (Chuang et al. 2005). Neighborhood characteristics which have a direct effect include the availability and offering of substances to adolescents (Crum et al. 1996) and the lack of informal social controls (Sampson 1992). In addition, living in a neighborhood characterized by drug abuse, unemployment, crime, and unresponsive police is psychologically distressing, and adolescents may drink and use drugs to regulate their anxiety and depression (Hill and Angel 2005). Buu (2009) reported that neighborhood instability was linked with the development of substance use and child psychopathology. Brook et al. (2011) found that environmental stressors were associated indirectly (by being mediated by individual stressors) and directly with tobacco and alcohol use among adolescents in South Africa. Living in disadvantaged neighborhoods also affects adolescent substance use via the family and peer contexts. However, Chuang and colleagues (2005) found that residing in a low-SES neighborhood was associated with increased parental monitoring and less tobacco use. It was also associated with increased peer drinking and increased adolescent alcohol use (Chuang et al. 2005).

136.2.4.3 School Risk Factors

Like neighborhood effects, the influence of school contexts on adolescents' substance use problems is both direct and indirect. For example, lack of enforcement of rules and low levels of school safety are directly related to students' substance use

(e.g., Reid et al. 2006). Mediating variables include the quality of the social networks (Mason 2010) and violent victimization (Reid et al. 2006). One school-related risk factor that is directly associated with substance use is academic adjustment (Ljubotina et al. 2004). In a cross-sectional study conducted among adolescents in Hungary, Piko and Kovacs et al. (2010) found that lower academic performance was associated with the use of legal drugs (tobacco use and binge drinking) and low school satisfaction and less communication with teachers about the use of illegal drugs. In another cross-sectional study conducted in Switzerland, Stronski et al. (2000) also found that better academic performance was associated with nonprogression to illicit drug use among adolescents.

In addition, a sense of belonging to one's school seems to act as a protective factor against substance use and abuse (Bond et al. 2007; Napoli et al. 2003; Rostosky et al. 2003). For example, Napoli and colleagues (2003) found that among Native American youth, a sense of belonging to their school was associated with lower levels of substance use.

136.2.4.4 Cultural Risk Factors

Numerous cultural factors can have an impact on adolescents' use of drugs, including levels of acculturation (Luengo et al. 2008), acculturative stress (Buchanan and Smokowski 2009), and cultural values (Soto et al. 2011). In the United States, it is generally found that among youth from immigrant families, those who are US-born and those who have lived in the United States longer use more substances than foreign-born adolescents and those who have lived in the United States for a shorter period of time (Epstein et al. 2001; Gfroerer and Tan 2003). However, this does not necessarily seem to be the case in other countries. An Israeli study compared adolescents who were born in the former Soviet Union to those born in Israel in terms of substance use (Isralowitz and Reznik 2007). The study found higher rates of binge drinking, current drinking, and ecstasy use among adolescents who were foreign-born.

Brook et al. (2003b) studied marijuana use in a cohort of Colombian youths and found that there was a relationship between earlier adolescent marijuana use and later adolescent problem behavior in a society in which drug use, crime, and violence were pervasive.

The direction and strength of the associations between acculturation and substance use thus vary depending on the context, as well as on the type of acculturation strategy adopted by the adolescent. Chédebois et al. (2009) found that three acculturation orientations (i.e., individualism, integration, and assimilation) were negatively associated with cannabis use among adolescents in France who had one (or more) parents who were foreign. The association between acculturative stress and substance use has been found to be mediated longitudinally by family relationships, internalizing and externalizing problems, and associations with deviant peers (e.g., Buchanan and Smokowski 2009) among Latino adolescents.

136.2.5 Gaps in the Literature: Future Directions for Research

136.2.5.1 Life-Course Perspective

In the past, research has focused on the period of adolescence in order to prevent substance use initiation or thwart its escalation, once begun. Despite the value of this approach, it does not take into account the long-term vicissitudes of substance use, i.e., the changing patterns of substance use over time, such as distinct trajectories of late starters, escalators, those who quit, or those who move into and out of substance use throughout the life course. Therefore, it would be important to study *within*-individual changes in risk and protective factors as related to *within*-individual changes in substance use and psychopathology at various developmental stages. A greater understanding of the longitudinal and concurrent risk and protective factors for substance use from several domains (the individual's personality, neurobiological factors, the family, the peer group, and contextual influences), and their interrelationships, should prove invaluable to informing both the content and the timing of prevention and intervention programs.

136.2.5.2 Multigenerational Studies

Multigenerational studies can also shed light on the etiology of substance use, psychopathology, and problem behaviors. A vulnerability to substance use may be transmitted via the adverse effects of parental substance use on parenting abilities, which, in turn, are linked with personality attributes in the child that are conducive to substance use (e.g., externalizing behaviors, low self-esteem). Further investigation of the specific mechanisms involved in the intergenerational transmission of substance use could help inform prevention programs.

136.2.5.3 Consequences of Adolescent and Young Adult Substance Use

Future research should continue to examine developmental trajectories (including comorbid trajectories) of adolescent substance use in relationship to key predictors and outcomes. Of particular interest are the following areas of functioning, which should be studied in conjunction with substance use histories: future research should examine a broad range of psychiatric diagnoses, including personality, mood and anxiety disorders, and impulse control disorders (e.g., pathological gambling), as outcomes of substance use trajectories in emerging adults and adults.

In sum, the identification of the consequences of persistence and cessation of substance use over this span of the life course will provide information crucial to the development and timing of intervention programs for substance-using adolescents and young adults. Understanding these relationships can help to clarify and validate theoretical models and may enhance efforts at prevention and treatment intervention.

136.2.5.4 Electronic Media

Technology has been advancing rapidly, and adolescents are becoming increasingly dependent on a multitude of media applications (especially social media sites such

as Facebook and Twitter) and devices (i.e., computers, tablets, and cell phones), as well as gaming systems (e.g., Xbox). A recent study in the United States found that on average, youth aged 8–18 years spend over 7 1/2 hours using entertainment media per day (Lamontagne 2010). Much of this time is spent using more than one electronic medium at a time, thus resulting in adolescents consuming an actual 10 hours and 45 minutes worth of media content each day. In addition, social media sites have become a means by which bullying behavior occurs among youth. Future research should examine the relationship between compulsive electronic media use and emotional and behavioral problems as well as a variety of addictive disorders.

136.2.5.5 Neurobiological and Genetic Effects

In recent years, technological advances (e.g., PET scans, *f*MRI) have contributed to a greater understanding of basic neurobiology, in general, and the effects of various substances on the brain, in particular. The findings of most gene-environment studies suggest that both genes and the environment, in combination or in interaction, play a role in addiction (Gelernter and Kranzler 2008). The study of gene x environment interactions has the potential to provide important implications for research and clinical practice. Increased knowledge resulting from such work may help geneticists better understand endophenotypes related to specific behavioral disorders, such as substance use. Genetic effects may be found to express themselves only under specific environmental risk conditions. Therefore, it is important to study epigenetic and genetic effects in adolescents exposed to certain psychosocial risk factors. Such work may yield information on the interrelation of genetic and environmental factors and substance use and dependence. Such research may also identify specific genetic factors which protect against psychosocial risk factors or which increase susceptibility to substance use. Studies of behavioral risk factors in connection with genetic studies may enhance understanding of the conditions under which psychosocial risk factors may result in the development of substance use and dependence in some, but not all, adolescents during the course of development.

Future studies should contribute to greater knowledge of the role of genetic factors in individual differences in sensitivity and exposure to environmental influences (e.g., Lynskey et al. 2002). Such knowledge is of great importance to help us understand vulnerabilities to addiction and the crucial role of gene/environment interactions in risk and protective processes (e.g., whether certain psychosocial factors may offset specific genetic predispositions to tobacco and drug abuse/dependence). Such work will contribute to the design and implementation of both prevention and treatment programs.

136.2.6 Implications for Prevention

136.2.6.1 Universal Prevention

Because of its biopsychosocial nature, the prevention of substance abuse must take place on several levels. Substance abuse is the phenotypic expression of the

interactions of a genetic predisposition(s) (genotype), psychosocial risk factors, and the psychopharmacological effects of the drugs used or abused. Also, other as yet poorly known factors, such as receptor activity, may play a role in the expression of substance abuse. As discussed above, the psychosocial aspects of substance abuse are rooted in the family, but also are located in the interactions and groups which individuals encounter, and the environments in which they spend their time during the course of growth and development.

Prevention must therefore begin in the family, preferably as early as possible. Families at risk may be identified by examination of several factors. These include (1) a family history of substance abuse, (2) the nature of the mutual parent-child interaction, (3) aspects of the marital or partner interactions, (4) the presence of comorbid psychiatric disorders or medical illnesses, (5) the presence of parental or familial psychopathology, (6) socioeconomic and cultural factors, and (7) aspects of the peer and sibling attributes and interactions.

Within the family, prevention may include (1) the provision of appropriate prenatal care; (2) parenting classes, especially for those families at risk; (3) marital counseling; (4) the treatment of psychiatric disorders or medical illnesses; (5) attempts to enhance the quality of the mutual parent-child relationship; and (6) efforts aimed at helping to improve the family's socioeconomic status.

Research has shown that some universal family-based interventions can be effective for preventing alcohol use (Foxcroft and Tsertsvadze 2011b) and the initiation of tobacco use (Thomas et al. 2008) among young people. Foxcroft and Tsertsvadze's systematic review (2011b) revealed that nine of 12 studies (with one being from the Netherlands and the remainder from the United States) showed significant positive intervention effects on various alcohol use measures among children and adolescents up to age 18 years. These interventions comprised psychosocial and educational programs that were delivered to parents and other caregivers with a view to having an effect on their children's alcohol consumption. Thomas et al.'s (2008) systematic review examined the effectiveness of interventions to prevent smoking initiation. Thomas and colleagues (2008) showed the greatest promise for family programs compared with controls but less promise when family programs were compared with school only interventions. In general, research reveals that early interventions are most effective (e.g., Carney and Myers 2012). Indeed, the 2001 United Kingdom (UK) report to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) emphasizes the significance of drug education beginning prior to the "age of onset" (Jeffrey et al. 2002).

Preventive interventions for tobacco use among young people can also be effective when delivered at the level of the community (Carson et al. 2011). In a systematic review which included 25 studies, ten were found to demonstrate positive intervention effects for community programs, with the most successful programs involving multiple components (e.g., with school and parental involvement), being of longer duration, having flexibility to enable adaptability to different contexts, having community involvement in elements of program development and implementation, and being theory-based (Carson et al. 2011). In the neighborhood, enhancing the work of prosocial community organizations,

support of neighborhood schools, efforts to diminish neighborhood crime and violence, and support for the provision of neighborhood amenities (such as stores, sanitation services, and other community resources) are most promising. In addition, mass media interventions may be effective for tobacco prevention (Brinn et al. 2010).

At a later point in the child's development, preventive interventions should embrace treatment interventions when appropriate and acceptable to family members. Such interventions could include family counseling, group and individual psychotherapy, and family-focused meetings.

There is also some evidence that multicomponent programs can be effective (Carson et al. 2011; Foxcroft and Tsertsvadze 2011a). In their comprehensive report, Frisher et al. (2007) concluded that improving the social environment of children as well as providing support for parents will "be the most effective strategies for primary prevention of drug use" (page iv). Interventions can have preventive effects when they focus on enhancing protective factors and diminishing risk factors. The treatment of comorbid psychiatric disorders in family members is especially important. Prevention programs for children and adolescents should be developmentally, culturally, and linguistically appropriate. As ethnic identification has been found to have strong protective effects (Burrow-Sanchez and Wrona 2012), attempts at strengthening ethnic identification can play an important role in preventive efforts and in helping treatment interventions to have further preventive and protective effects.

Adolescence is a crucial time for efforts to prevent or diminish substance abuse, as the precursors of most substance abuse begin by early or mid-adolescence (Dennis and Scott 2007; Tarter 2002). Adolescence involves a number of significant biopsychosocial and maturational changes, including separation from parents, closer attachment to peers, the psychosexual changes of puberty, the development of sexuality, the development of autonomy, and the growth of interest in the choice of a vocation. Because adolescence is the most common period of onset for the use of illicit drugs (Swendsen et al. 2012), it is therefore the most opportune time to use preventive interventions to help adolescents go through this period, marked by many stressful changes, without turning to the use of illicit drugs. Such preventive programs should focus on the enhancement of protective factors as noted above, such as a strong mutual parent-child relationship, ethnic identification, the treatment of comorbid psychiatric disorders, and the encouragement of involvement with prosocial peers.

Universal prevention programs are often delivered in school settings, although evidence of the effectiveness of school-based programs is less compelling than that of interventions delivered in family and community settings. Reviews of school-based universal programs indicate that some programs can lead to reductions in the use of alcohol (Foxcroft and Tsertsvadze 2011c), tobacco (Thomas and Perera 2013), and illicit drugs (Faggiano et al. 2005) among adolescents, although certain approaches are more effective than others. For example, the life skills training approach in the United States, the social influence approach (the Unplugged program) in Europe, and a program focusing on classroom management

(known as the Good Behavior Game) in both Europe and the United States had the best evidence for reducing alcohol use (Foxcroft and Tsertsvadze 2011c). For tobacco use, certain intervention elements and approaches, namely, delivery by adults rather than by peers, and social competence and social influence-type approaches were most important. Finally, for illicit drug use, skills-based interventions have been found to be the most effective in preventing various types of drug use behaviors (Faggiano et al. 2005).

136.2.6.2 Selective Programs

Selective programs should focus on prevention among adolescents who are at high risk of developing substance use-related problems. Many of the psychosocial origins of substance abuse in adolescence often are found in family interactions, as well as in many of the groups which form during growth and development (Vakalahi 2001). Therefore, prevention of adolescent substance abuse can include a number of different prevention approaches. For example, mentoring programs among high-risk groups can be effective (Thomas et al. 2011). Thomas et al.'s (2011) review showed that mentoring programs can be particularly effective among minority and "deprived" adolescents for preventing the initiation of alcohol and other drug use.

Medications may be used to treat any underlying pathophysiological predispositions, as well as any comorbid psychiatric disorders, which are found in a large percentage of substance abusers (Compton et al. 2007; Pettinati et al. 2013). Adverse environmental and familial factors may be prevented by interventions focused on changing the risk and protective factors for substance abuse which have been discussed previously in this chapter. Group and family interventions target adverse interpersonal interactions and also seek to prevent the adverse behavioral effects of the drugs themselves with emphases on diminishing craving and fostering relapse prevention and rehabilitation. Prevention programs that combine several types of psychosocial interventions often prove to be most effective.

Adolescent substance abuse prevention can occur in a variety of settings, including outpatient programs, schools, and churches, among others. The level of care should reflect the needs of the particular adolescent and her/his specific context (e.g., peer group, family, and neighborhood). Adolescent prevention may call for repeated efforts over a long period, and the prevention approach may vary depending on the needs of the adolescent at a particular time. A general rule is the longer the adolescent remains in prevention programs, the more effective the prevention and treatment (e.g., Latimer et al. 2000). Positive prevention effects may, and hopefully will, take place, even after the termination of the specific program (Hubbard et al. 2003).

It is important in the prevention of adolescent substance abuse that prevention interventions are developmentally and culturally appropriate (Whitbeck et al. 2012). The timing of each particular intervention should be synchronized with each adolescent's particular psychosocial context, as well as with her/his stage of development. As an example, in early adolescence, it is important to intervene with the parents and the child to focus on their relationship, but in later adolescence,

interventions might focus more on peer issues or on specific adolescent issues in adolescent groups.

The importance of cultural issues in prevention cannot be overstated. Cultural variations in each psychosocial domain must be factored into prevention. Cultural differences in important domains, and in their meanings, can be found across different ethnic and racial groups. The individual conducting the prevention program must understand and respect such differences and must include them in a sensitive way in any prevention program. Different cultures may view psychosocial interventions and therapy in different ways, and awareness of such cultural issues, combined with interventions that are culturally and linguistically competent and appropriate, is important for intervention effectiveness (e.g., Whitbeck et al. 2012).

136.2.6.3 Indicated Programs

For adolescents who have already started using substances, but who do not yet meet abuse or dependence criteria, indicated programs can be implemented to halt such progression. At the individual level, individuals who are already experiencing problems can be assisted via various programs. For example, interventions with elements of motivational enhancement approaches or transtheoretical model interventions where individuals' degree of readiness to change is taken into account can be effective for smoking cessation among adolescents (Grimshaw and Stanton 2010). Community-based interventions (harm reduction, syringe exchange for injection drug use and various outreach activities) can serve to minimize the chances of the behaviors becoming entrenched.

136.3 Conclusion

This chapter summarizes findings from several recent studies which have examined the psychosocial risk and protective factors for drug use and drug abuse using a developmental approach. This approach, based on Family Interactional Theory (FIT), focuses on the role played by the parent-child relationship and, particularly, aspects of the non-conflictual mutual attachment relationship between parents and child. According to FIT, the parent-child mutual attachment relationship is of special significance in preventing the development and maintenance of risk factors for drug use. The chapter examines risk and protective factors in several psychosocial domains, with special emphasis on the developmental pathways leading to the presence of both risk and protective factors for drug use, starting in childhood and continuing in adolescence. The chapter has also focused on research which has examined the risk/protective and protective/protective interactions among psychosocial factors related to drug use/abuse. In the design of preventive or treatment interventions, it is especially important to consider the total psychosocial environment of the adolescent. The various psychosocial domains have complex interactions with one another, and so it is of great importance to strengthen protective factors (e.g., enhanced family functioning) in those domains and interactions that

will be the most effective in mitigating risk factors, as well as in those which have been shown to directly affect the adolescent's substance use. In addition, effective interventions must be developmentally, as well as culturally, appropriate. These fundamental findings, taken together, indicate that preventive and treatment interventions for adolescent substance abuse should be designed for different adolescents, considering their psychosocial and cultural environments, as well as their developmental level. Treatment itself can be preventive.

Although research efforts have clearly specified particular psychosocial risk and protective factors involved in adolescent substance use and abuse, there are a number of questions which remain to be answered by future research efforts. To begin with, current knowledge of the genetic bases for substance abuse is quite limited, and more needs to be done to expand knowledge in this area. Variations in specific genes that affect risk or protective factors for substance use/abuse must be identified in order to enhance clinical applications of knowledge. In addition, interactions between genetic vulnerabilities and environmental factors must be explored further, with assessments of both gene-environment and gene-gene interactions needed. In order to carry out these assessments, improvements are needed in identifying and accurately measuring varying aspects of the individual's environment through the use of innovative and creative research efforts. By focusing on these challenges, we can bring about the development of a more accurate biopsychosocial perspective of the development of adolescent substance abuse.

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ADHD and Substance Abuse

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Sam Chang

Contents

Abstract

The interaction and relationship between attention deficit hyperactivity disorder (ADHD) and substance use disorders (SUD) have long been recognized. Many hypotheses for this relationship have been advanced. However, it took contributions from many fields to shed light on this very prevalent problem, often starting in late childhood or early adolescence but continuing well into adulthood. These included contributions from epidemiology, genetics, neuroimaging, psychopharmacology, and of course long-term clinical follow-up to understand that SUD and substance abuse are significant complications of the lack of adequate treatment of ADHD, often dating from early childhood. There is also a bidirectional influence, esp. with the use of tobacco and alcohol during pregnancy increasing the risk for the development of ADHD in the fetus. That ADHD and SUD are public health issues is now well recognized and has resulted in formal clinical trials to elucidate the best treatment when both disorders co-occur or are concurrent/comorbid. This is particularly relevant as treatment of ADHD is often with medications with a risk of diversion and hence abuse. As such, clinical trials to understand the relative benefits versus risks are very

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important clinically. A review of the literature in these areas leads then to an attempt to translate research findings into evidence-based practice that maximizes benefits but minimizes risks. Practice guidelines in this respect are reviewed.

137.1 Introduction

In North America, the presence of SUD earlier into adolescence and even childhood is increasingly being recognized and responded to by various prevention, early identification, and treatment programs. These programs were plagued by lots of initial uncertainty and skepticism as to even the validity of the diagnosis of SUDs in the adolescent population. This was also the case for the efficacy of various programs of prevention and treatment (Substance Abuse and Mental Health Services Administration 2010). These are now far better understood including the confounding presence of developmental comorbidities, especially increasingly by the presence of another major childhood psychiatric disorder, that of ADHD (Biederman et al. 1993). It has been known for some time that ADHD is a very significant pediatric disorder from a prevalence standpoint (Offord et al. 1989) but also of its negative influence on functioning needed for successful child and adolescent development (Barkley et al. 1991; Klassen et al. 2004). We are finally now more aware as to its *influence* in terms of etiological and possibly pathophysiological factors esp. in the development of SUD. In fact, we are more and more aware of the influence of ADHD in the development of the *disruptive behavioral disorders* (Jensen et al. 1997) and of its profound role and cost not only to the individual but also to the family and in particular to society as a whole (Pelham 2007). This knowledge has lead to ADHD being labeled as a *public health issue* in some countries, due to its high prevalence, high cost and sequelae if untreated, and the efficacy of available treatments (Rowland et al. 2002; Centers for Disease Control and Prevention). This suggests the issue is not one just to be dealt with by physicians and their patients but also by larger government policy and societal attitudinal shift. ADHD is also a worldwide phenomena, present in all areas of the world where it has been studied (Farone et al. 2003; Polanczyk et al. 2007). It also has one of the highest interrater reliability of diagnoses in the DSM (Freedman et al. 2013). Its presence in adults has now been well established in well-conducted epidemiological studies (Kessler et al. 2006) and has been estimated to have a prevalence of 4.4 %. Finally, it is now generally accepted that medication treatment results in protection for the development of SUD in meta-analysis (Wilens et al. 2003). At worse, some longitudinal studies have demonstrated that medications for ADHD have a neutral effect for the protection and for the causation of SUD.

In this chapter, we will try to review some of the more significant developments from ADHD research and of its connection to SUDs, not only in adolescence but down into childhood and forward into adulthood. This will illustrate the costs and the benefits of treatment of this very prevalent and costly psychiatric disorder first developing generally in childhood.

137.2 Clinical Correlates

137.2.1 Diagnosis

Even in countries officially using the ICD system of diagnosis, the Diagnostic and Statistics Manual of the American Psychiatric Association, now in its fifth edition, is used and widely accepted as the most useful criteria clinically. DSM 5 has made improvements for the diagnosis of ADHD in adults (DSM 5 2013). These include symptoms fitting better with the adult experience versus the previous child-based ones. There is also a recognition of symptomatic evolution into adulthood by a slight relaxation of symptomatic recall by a change to an onset by age 12 from age 7 and the number of symptoms required as an adult.

There are also free rating scales available. These include the ASRS (Adult Symptom Rating Scale) of the WHO. This scale is composed of two parts. Part 1 has the best predictive value for the diagnosis of ADHD. Part 2 is also helpful to elucidate the additional symptoms needed for the diagnosis. Although it is a self-report rating scale, it is best used in conjunction with the clinician to build rapport and to fine-tune for more specific symptoms and especially for functional impairment. This not only is important for the diagnosis but then becomes the focus and target of treatment. As in all rating versus diagnostic scales, its real strength is in follow-up where symptomatic and functional improvements can be followed and quantified to optimize and fine-tune the treatment process. Our ultimate goal of course is not to just improve symptoms and functioning but to normalize it, i.e., to treat to *remission* as in other psychiatric disorders such as major depression. There is also the availability of free child and adolescent rating scales, again for the key purpose of following and quantifying the course of treatment. The scale often used for this purpose includes especially the SNAP IV parent and teacher scale. There is a full SNAP scale useful for the screening of the most common major comorbidities of ADHD. There is also a short SNAP IV 26 and a very similar Vanderbilt University Scale, both of which encompass only the 18 DSM symptoms (nine for inattention and nine for hyperactivity/impulsivity) as well as the eight symptoms for oppositional defiant disorder (ODD). This is due to the very frequent clinical and research finding of the presence of ODD as the most common comorbidity of ADHD (The MTA Co operative Group 1999). Also very frequently noted is that successful treatment of ADHD medically also greatly improves and often drives the ODD also into remission (The MTA Co operative Group 1999; Elia et al. 2008). This is especially important in the case of concurrent SUD since the disruptive behavior disorders are so commonly also comorbid with SUD. While the SNAP 26 and the Vanderbilt Rating Scale also come with a scoring guide, a very commonly used method clinically to score this is to aim for symptoms to be in the *not at all* or *sometimes* columns but not in the *often* or *very often* columns. As the *not at all* or *sometimes* columns denote normal functioning, we are in fact advocating for *normalization* or *remission* of symptoms as the treatment goal. To further aid the computerized office or computer-literate patient and physician is the availability of a website "adhd*ratingscales.com*" which aids the physician and the family to be

able to log in and do the rating scales online. This way, teachers and parents can do the rating scales wherever they are and have web access. The physician once he or she has registered gets an e-mail of the scale which is prescored thereby saving this often tedious and time-consuming task. The website is secured and only for the use of registered physicians and their patients.

ADHD Rating Scales – Available Free:

- **Adult Self-Report Scale (ASRS) – WHO** http://www.adhdawarenessmonth.org/wp-content/uploads/adult_adhd_checklist.pdf
- **SNAP-IV 26 – Teacher and Parent Rating Scale** http://www.caddra.ca/pdfs/caddraGuidelines2011_Toolkit.pdf
- **SNAP-IV 90 – Teacher and Parent Rating Scale** http://www.shared-care.ca/files/SNAP_IV_Long_with_Scoring.pdf

137.2.1.1 Associated Symptoms

Other than the three core areas of symptoms, i.e., inattention, impulsivity, and hyperactivity, there are also frequent areas of associated symptoms that are important to recognize as these can become very critical clinical areas for treatment if optimal functioning is to be gained. One of the most key areas especially for those whom are also suffering from SUDs is the area of sleep or, more specifically, the relative lack of sleep or of poor sleep.

Sleep

Patients with ADHD often complain of poor sleep (Owens 2005). The usual complaint is of phase-shifted sleep where, at the usual bedtime, the patient is *not tired* or *too revved up* or *thinking too much* to be able to wind down and get to sleep. As a result, the patient often uses electronic audiovisual equipment, e.g., TV, computers, and, worse of all, video gaming. This then results in very late nights and hence the inability to get up in the mornings. Very often the patient blames the medication (usually a stimulant) for *keeping me up at nights*, yet, upon closer history taking, we then hear the patient has never been a good sleeper and has always had problems falling asleep. This is a major problematic area for several reasons. First is the expected problems focusing when tired thus compounding the deficits from the underlying ADHD. Secondly, as ADHD patients are far more prone to addictions of all kinds including behavioral addictions, the risk of video gaming addiction becomes much higher, again compounding the patient's already compromised level of functioning (Weiss et al. 2011). In fact, it is not uncommon for the *video gaming addict* to spend every waking moment playing videogames so that even self-care and activities of daily living are compromised, not to mention work, school, or relationships.

Thirdly, the poor sleep often results in the use of substances, typically cannabis, at night time in order to facilitate sleep (Conroy et al. 2010). This self-medication strategy is especially concerning, as we have become more aware that if we are unable to help our SUD patients with sleep, then sobriety is likely to be compromised and short lived. Thus, this associated ADHD

symptom is especially critical for patients with ADHD and SUD to get under control and, quickly, if they hope to be successful in both sobriety and also functioning.

Short Tempered, Easily Frustrated, and Stressed

This is the common complaint of the family of the patient with ADHD (Wehmeier et al. 2010). The patient may or may not be aware of this, but, nevertheless, it is a major reason for dysfunction especially in areas where there is social interactions like school and work and of course within the family system. This associated symptom is in fact a big part of the reason why adults with ADHD are often misdiagnosed to have bipolar disorder. Of course, bipolar disorder is a relatively common comorbidity of ADHD and "co-segregate" in other family members (Faroane et al. 1997; Klassen et al. 2010) and increases greatly the relative risk for SUD over and beyond that of ADHD alone. This group of patients is among the highest risk group to develop a SUD. However, ADHD individuals do not present with the usual endogenous cycling of bipolar disorder but with chronic developmental easy irritability and frustration due to environmental stressors. There are also no episodic euphoric, manic, and psychotic symptoms. The differential diagnosis here includes ADHD with concurrent substance abuse resulting in cycling moods and psychotic symptoms. It is now quite obvious why those with ADHD whom are in the early stage of substance abuse treatment and likely to be withdrawing, or the video gaming addict with ADHD and trying to cut back, can be so oppositional and difficult to deal with. In fact, in our Adolescent Concurrent Disorders Program in Calgary, this is the group of patients most likely to require the highest level of parental support for behavioral containment and pharmacological intervention for their often out-of-control behaviors.

Risk-Taking/Thrill-Seeking Behaviors

This is an associated symptom which is the costliest to society and is one of the major causes of crisis and containment of the adolescent. It is also often inextricably tied into substance abuse. In its extreme form it can lead to the development of a conduct disorder and can predict ongoing criminal behaviors. Conduct disorder in fact is the risk factor that confers the highest risk for a SUD in adolescents (Molina et al. 1999). The actual behavioral manifestations of this associated symptoms has a lot to do with the psychosocial milieu of the child and adolescent. In particular, if appropriately channeled, this can become a very prosocial strength of the ADHD individual and can be the source of much self-confidence and self-esteem. The individual will then be conferred status and respect. On the other hand if inappropriately channeled, there is a very high risk of the development of antisocial behaviors which can lead to permanent underclass status.

As an example, there are lots of ADHD children and adolescents whom have gained lots of skills and status and confidence and esteem from involvement in athletic activities (Halperin and Healey 2011; Verret et al. 2012).

ADHD individuals often do better in individual or parallel pursuits versus in a team setting. They enjoy and often excel in thrilling sports, e.g., ski racing and ski jumping, mountain and BMX *trick* biking, mixed martial arts, boxing, etc. The key to good outcomes is involvement in a structured program rather than ad hoc on one's own. The alternative if these more prosocial activities are not available, such as due to poverty or systemic family instability, may be the enveloping of the ADHD individual into the antisocial world of substance abuse and criminality and a gradual isolation of oneself into the criminal world. Due to the immersion of the adolescent or young adult in these alternative values, there is great risk of their leaving to join the *street life* or being kicked out of the parental home due to the intractable nature of their negative behaviors and associates. Worse would be arrest and incarceration to fully ostracize them and to solidify their identity as part of the criminal underclass.

137.2.1.2 Pathophysiology

The numerous connections between ADHD and SUD become far clearer once we understand the likely pathophysiology of ADHD. Awareness of the pathophysiology of ADHD will also give us hints and understanding not only of the core symptoms but the source of much of the dysfunction, associated symptoms, and comorbid risks of ADHD. Finally, it will also give us insights into what is most likely to be effective treatment strategies especially when we take into account the neurophysiological effects of treatment itself.

Familial and Genetic Risk

ADHD has long been known to be a familial disorder with much higher risks especially among first-degree family members (Cantwell 1972; Epstein et al. 2000). This of course begs the question of whether it is genetic or environmental risks which bring out the symptoms. Unfortunately, like many non-Mendelian polygenetic influences, it is unlikely to be totally the result of genes or environment but rather a combination of the two.

One of the methods to elucidate the role of genes versus environment is to compare the likelihood of the presence of a disorder in first-degree relatives in biological versus adoptive families. Results of this demonstrate a much higher likelihood of ADHD in biological first-degree relatives of a proband compared to adoptive relatives. It is also higher the closer related one is, for example, the risk of biological siblings having ADHD if the proband does is even greater than the risk for biological parents (Sprich et al. 2000). An even more precise method is to compare the differences between monozygotic versus dizygotic twins. As the twins share the environment similarly, including the in utero environment, differences in rates of ADHD are felt to be much more of a precise measurement of the relative risks of environment versus genes. A meta-analysis of the literature in this regard shows a *heritability index* of 0.76 (Faraone et al. 2005) (where 0 is no genetic influence, i.e., all environment, and 1 is all genes and no environmental influence). This compares with other medical disorders of around 0.4 for asthma and breast cancer and around 0.5 for depression and the very heritable psychiatric disorder of

schizophrenia of 0.7. Among heritable traits rather than disorders, height is very heritable at about 0.9.

Heritability is of course a measurement of overall genetic risk. As one would expect, we are not looking at a single but multiple genes (Faraone et al. 2005). Though none of the risk genes are able to give us a causal statistical threshold of 10^{-9}, as demanded by geneticist, they at least give us numerous clues to the pathophysiology and possible treatments. That most of the genes are connected with the well-functioning and intricate balance of the dopaminergic modulation system, and most effective treatments also are directed at this system, and, of course, that this system is implicated in addictive disorders all point in the same direction. One of the most interesting of these genes is the DRD4-7 repeat allele gene, which is also known as the *thrill-seeking gene*. People with this genetic variant have a lower dopaminergic tone and a much higher tendency to risk taking behaviorally. This may account for the associated thrill-seeking symptoms in many of those with ADHD as well as the very high comorbidity with oppositional defiant and conduct disorders. This may also account for the increased presence of substance abuse and criminality in ADHD individuals. One must be reminded, however, these risk genes do not mean the individual is going to be a criminal or drug addict, as there are very many modifiable psychosocial risk factors as well.

Perinatal Risk Factor

We are now beginning to understand how gene and environment interact to cause disorders. One of the most potent developmental periods when the environment may exert its maximum influence is in utero. As development is at its maximum at this point in the individual's life span, it becomes the point at which negative or positive environmental influences will exert its peak effect. In this perinatal period the key environmental influences that may negatively affect the fetus is the presence of maternal drinking of alcohol or of maternal tobacco smoking (Mick et al. 2002). Both of these in utero influences are risk factors for the development of ADHD. Alcohol especially can often result in fetal alcohol spectrum disorder (FASD), which, besides neurodevelopmental and physical sequelae, often also results in quite severe and intractable ADHD. There is even some evidence that paternal alcoholism can worsen and exacerbate the result of maternal in utero drinking (O'Malley 2007). There is also the observation that even in the absence of maternal drinking, the FASD parent may still pass on some of the disabilities and features of fetal alcohol in a phenomenon now labeled as epigenetics. As if all of these risks are not enough, nicotine exposure in utero further increases the risk for the development of ADHD (Milberger et al. 1996; Neuman et al. 2007). Tobacco use is also an independent variable for the development of SUD (Clark et al. 1998). We are also aware that ADHD individuals have a much higher risk of early onset of nicotine abuse (Milberger et al. 1997). This then predisposes to the early development of SUD due to the negative influences of like-minded peers, all of whom value independence from adults more than success (Marshall et al. 2003). These peers also tend to not being able to delay gratification, hence exacerbating risk-taking behaviors. So now we come full circle with ADHD individuals at

risk for SUD and the SUD worsening the next generation's outcome. This is especially the case with assortative mating which we know to be quite common clinically, i.e., both spouses being addicts and both with a much higher likelihood of having ADHD.

Psychosocial factors have also been shown to further increase the risk of ADHD. These include a combination of maternal psychopathology, paternal psychopathy, and early separation from family, e.g., apprehension by child welfare authorities, large sibship sizes, lower social class, and severe marital discord. These findings from the landmark *Isle of Wight Study* by Sir Michael Rutter et al. (1975) indicate just how potent are the psychosocial and genetic variables acting in concert, to the point that one can *predict* later psychopathology even in the young child. Together with our newfound knowledge of epigenetics and the *teratogenic* effects of alcohol and tobacco, we now have a very powerful breadth of knowledge to decrease the burden of psychiatric disorders. The good news as always is tapered by the bad news that effective prevention requires not only knowledge but wisdom in applying into public policy what we know to be true in science. Alas, this wisdom is not quite as easily gained as knowledge, so we remain unable to exploit much of what we know to minimize individual and family morbidity and, yes, mortality.

Neuroimaging/Neuropathophysiology

One of the biggest impediments to a better understanding of psychopathology until recently was the lack of tools to visualize not just structure but neuroreceptors, neuroconnections, and neurofunctioning in the living and working, active brain. Fortunately with the availability of MRI, fMRI, Diffusion Tensilar Tomography, SPECT and PET scanning, and on top of the old stalwart CT and EEG and with genetic techniques like the breeding of the *genetic knockout mice* animal models and Genome-Wide Association Studies, a wealth of new understanding of the workings of the normal and psychopathological brain has emerged. In fact, the first published PET scan for psychiatry was in ADHD, specifically parents of children with ADHD whom exhibit ADHD symptoms themselves (Zametkin et al. 1990). This prevented children from exposure to radiation but allows studies of the underlying ADHD in the functioning brain. As a result, we knew very early on that ADHD seemed to be related to a disconnect between the higher cortical centers which tended to be noradrenergic, with the lower striatal structure which were dopaminergic. Thus, this *noradrenaline-dopamine axis* was postulated to be the problem in ADHD. It was certainly backed up by the treatments already prevalent at the time, i.e., of stimulants that exerted its effect on both the noradrenergic and dopaminergic systems.

The other piece of knowledge needed was how the stimulant medications, in use for ADHD for more than 70 years, actually worked. Again with PET scanning we were able to use radioactive ligands to block the postsynaptic dopaminergic receptors (Matochik et al. 1993). Once a stimulant like methylphenidate was given, the level of dopamine or the dopaminergic tone was inferred to increase by the displacement of the radioactive ligand. This was via the action of methylphenidate

in blocking the presynaptic dopamine reuptake transporter. To close the loop, once the dopamine tone increased, symptoms of ADHD decreased clinically.

Further studies to visualize the anatomical effects on the brain of these microscopic neuroreceptor activities via fMRI were successful once the situational load on the brain was controlled. For example, when the brain was given an inhibitory task (Counting Stroop test), then those with untreated ADHD showed an inability to activate the anterior portion of the anterior cingulate cortex compared to normal controls (Bush et al. 1999). That effort was being exerted by the ADHD patients was obvious, as they activated a much larger portion of the brain than controls in an effort to complete the task but in a grossly inefficient and hence ineffective way neurologically. Once the ADHD patient was treated, this finding on fMRI disappeared indicating successful treatment of dysfunction and hence symptoms. This also dovetails very well with the associated symptoms of short temperedness. The posterior portion of the anterior cingulate is the emotional regulation center, thereby subjected to input from the anterior cingulate (Bush et al. 2000). It is for this reason that one of the best treatments for short temperedness is optimal treatment of the underlying ADHD and especially with stimulants.

In regard to SUD, one of the most intriguing findings was recently at the NIDA, where untreated ADHD individuals, so untainted by any possible medication effect, were found to have lower dopaminergic tone in the nucleus accumbens (Volkow et al. 2009). Since the nucleus accumbens is part of the primitive reward pathway that is implicated in addictions and activated not only by drugs of abuse but also by behaviorally addictive behaviors, this seems to connect neurophysiologically the observation of the heighten risk of addictions and thrill-seeking behaviors in the untreated ADHD individual.

Psychostimulants increases dopaminergic tone and hence increases saliency of a task for the individual. At the same time, if presented with a gradually increasing concentration of psychostimulants, such as via oral dosing, there is no euphoria, whereas if dosed with an IV bolus, then indeed euphoria was noted. This observation further brings us to a treatment strategy to minimize the risk of medication diversion and abuse by using the newer long-acting psychostimulants which has much lower abuse potential due to difficulty in the hands of the addict to defeat the slow release mechanism, hence preventing euphoria by not being able to load a large enough amount of stimulant, e.g., by snorting intranasally or using via IV means (Volkow and Swanson 2003; Volkow 2006). We will discuss these strategies in more detail later.

Finally, there are numerous studies (Bush et al. 2005) documenting volumetric decreases in various parts of the brain ranging from cerebellum to prefrontal cortex to inadequate connections via various nerve bundles and tracts and even decreased cortical thickness. There is even a very elegant developmental prospective study by the NIMH demonstrating developmental delay and immaturity in the untreated ADHD child brain compared to controls (Shaw et al. 2007). However with treatment, there is an acceleration of development to almost the level of controls. This is one of the first neurological evidences that ongoing treatment may be a very good

prophylactic and prevention strategy for the complications of untreated ADHD. It also backs up findings from clinical studies and demonstrates physically that there is risk of significant side effects to NO treatment and that the common strategy of "waiting to see if he grows out of it" may be causing much harm and has lifelong sequelae not only clinically but also neurologically.

Risks of No or Inadequate Treatment

In medicine, as in much of life, decisions are made by a balance of the risks and benefits of treatment versus no treatment. To take an extreme example, if one has been diagnosed with a condition like cancer, before embarking on tumor removal surgery, chemotherapy with cytotoxins, and radiation therapy with ionizing radiation with all of these concomitant side effects, one would want to know the risks of no treatment and the chances of success. We of course know the ultimate risk is death for no treatment in cancer. As a result one is willing to accept a far higher risk for treatment side effects than if the condition had a lower risk than death.

This is the same thinking behind the treatment of ADHD. Unfortunately much emphasis has been placed on possible side effects of treatment, which is present in all areas of medicine and not enough on the risks of no treatment (Shaw et al. 2004). The first most obvious risk is in school. Children with ADHD have been noted to have much higher rates of academic failures and underachievement once corrected for intelligence than controls (Barkley et al. 2008). This is easily understood in ADHD due to the effects of inattention and easy distractibility to one's academic performance. The presence of distractions especially in a classroom has a very deleterious effect on academic outcome to an ADHD child. The presence of hyperactivity and impulsivity that often is present further adds to academic risk. Furthermore, the presence of executive dysfunction, commonly present in ADHD, contributes greatly to academic underachievement especially in the more advanced grades like in high school. This includes skills like organization, planning, prioritizing, and inhibition, which take on more importance as one matures and expectations are increased from adults (teachers and parents) to take on more of these skills in one's own life. Finally, there is often the presence of problems in motivation, likely due to intrinsic deficient dopamine tone in the reward system (nucleus accumbens) (Volkow et al. 2009).

Though good academics are a very major portion of one's school success, it is by no means the only variable. Social peer interactions are widely accepted by educators as a very significant part of the school experience.

Children themselves also place a large premium on the effects of social interactions to their overall school success. Here as well, the ADHD child is in a significant disadvantage (Strine et al. 2006). The effects of impulsivity are felt most acutely here. Here the child often *acts without thinking*, hence inadvertently offends another child. Add the inattention and distractibility as well as often hyperactivity, and one can easily imagine how other children often perceive the ADHD child as unruly and unpredictable. Add to this the frequent presence of impatience and the poor ability to pick up nonverbal cues so essential to social interactions, and it is no wonder that ADHD children report less friends and less positive social interactions, not only with peers but even with family members.

The final functioning that predicts success at school is the ability to deal with authority relationships. The ability to work with teachers, lunch room supervisors, principals, and other adult *authority* figures is vital to a child successfully negotiating school. Here impulsivity and hyperactivity again contribute very greatly to a poor outcome. However, the worst characteristics with the authority figures are the very frequent presence of an oppositional defiant disorder (The MTA Co operative Group 1999). This habitual surliness, passive opposition, and active defiance of authority that is the top comorbid disorder to ADHD is a major contributor to the poor experience ADHD children have at school and also at home, since the same behaviors are directed at parental authority figures as well. It is no wonder then a major risk of untreated ADHD is the significantly increased rate of lack of completion of high school and lower college graduation rates (Barkley et al. 2008). This of course has major implications for the longer-term socioeconomic achievement of the ADHD child and later on by his or her own family.

Due very much to the same interactions of inattention and distractibility, impulsivity, restlessness, and impatience, together with passive opposition and active defiance, one of the other major risks of untreated ADHD into adulthood is the high frequency of being terminated at a job. This then results in the affected individual having to seek multiple jobs and careers. This is not only stressful and impacts one's emotional and relational health but, at a very basic level, results in a lower income, employment reduction, and increase in social assistance (Barkley et al. 2008; Fletcher 2013).

Given these significant consequences psychosocially of untreated ADHD, it is surprising to know that frank psychiatric comorbidities, e.g., mood disorders (both unipolar and bipolar), anxiety disorders, and personality disorders, are increased in those with untreated or poorly treated ADHD. In fact, one can actually make the statement that in a well-treated individual with ADHD, we can *prevent* or *decrease the risk* of development of psychiatric disorders as the individual develops over time (Beiderman et al. 2009).

Other risks very relevant to Addictions Professionals are the increasing awareness of the risk of addictions with untreated ADHD. In both prospective follow-up and meta-analysis, those with untreated ADHD are at significantly increased risk (2×) over a lifetime of developing a substance use disorder (Wilens et al. 2003). This is also part of the reason that patients with untreated ADHD are far overrepresented in prisons. Studies of the prison population have found about 15 % of prison inmates to have persisting ADHD and up to 50 % having a childhood history of ADHD (Young and Thome 2011). In fact, the cost of housing and providing for prison inmates is one of the biggest societal costs of untreated ADHD.

Costs of untreated ADHD are one of the major unrecognized consequences (Bernfort et al. 2008). That the costs are paid by every level from the individual to the family, to businesses, and to the overall society and government is even less recognized. Of course, the individual suffers from ADHD and its attendant comorbidities, e.g., depression, anxiety, and substance abuse. However, these

have cost businesses and the community to the tune of billions of dollars in the USA per year.

Families of those with ADHD also paid the cost (Cussen et al. 2012). The families have a higher rate of marital discord and separation; primary caregivers often change their work status upon diagnosis to help deal with the fallout of ADHD; there is more likelihood of unwed pregnancy and contracting STIs; children given up for adoptions are more often from a parent or parents with ADHD.

Driving is also increasingly recognized as a major societal cost of ADHD (Barkley et al. 1996). Untreated ADHD patients are noted to have more speeding tickets, motor vehicle accidents, and road rage and drive without a license. In some jurisdictions, physicians are obliged to report any patient with ADHD who drives while unmedicated. Driving studies in simulators have found untreated ADHD drivers to commit more errors both of omission and commission (speeding) especially in long boring and unstimulating roads. Interestingly, driving a manual transmission seems to be helpful, likely due to the increased involvement and hence saliency of one's actions to the untreated ADHD individual.

Given the costs of untreated ADHD, i.e., financially, socially, educationally, occupationally, familially, parentally, and psychiatrically, is it any wonder that untreated ADHD confers such a high risk for the development of a substance use disorder? Many of the risks of untreated ADHD are the same risk as for the development of substance use disorders. In this authors' program, the genogram is used as an agent of both neutral information gathering and engagement. We have noted this very strong familiarity of addictions over the generations. With the data present thus far, it is the considered opinion of this author that much of what is noted via a genogram for addictions is actually merely the development of consequences of untreated ADHD in vulnerable genetic populations. The genetic vulnerability is then activated by the very real psychosocial disadvantage and hence stressors that untreated ADHD confers.

137.2.1.3 Treatment

MTA Study

Fortunately, with the advent of the large multisite, multimodal treatment studies, so as to be able to study the relative contributions of various modalities of treatment, we now have a far better understanding of the merits of various treatments (1999). The first and still key study of this type in this field was the Multimodal Treatment of ADHD (MTA) study of the National Institute of Mental Health. This study firmly established the efficacy of treatment for ADHD and especially of medication treatment.

In this landmark study conducted under the vision and leadership of Dr. Peter Jensen of the NIMH in both Canada and the USA, children with ADHD were admitted to the study with very few exclusionary criteria especially in regard to other psychiatric disorders. This had the advantage of allowing a typical clinical population rather than the usual monodiagnostic homogenous study population. The children were then randomized to one of four treatment groups; these were as follows:

Usual Treatment

This meant what was usually done at the time, i.e., seeing a physician and being prescribed Ritalin b.i.d. and with long duration between follow-ups.

Psychosocial Treatment

This was using all empirically useful psychosocial treatments and combining them in such a way as to maximize their efficacy. These included such interventions as summer social skills camps, academic remediation and support, parent skills training, etc. This was the most expensive arm of treatment.

Intensive Medication Treatment

This arm consisted of each child being given the optimal dose of stimulant to not only improve but treat to remission all ADHD symptoms with full coverage medication throughout the waking hours. Given the medications available at the time, it was of t.i.d. use of stimulants. Symptoms were also followed systematically with a rating scale. Follow-up was also on a regular basis with a psychiatrist. Compliance was also ensured with regular contact.

Combination Treatment

This arm essentially combined the psychosocial and intensive medication treatments.

In total 579 children were enrolled and followed with treatment for a period of 14 months, which even for today is an uncommonly long duration of follow-up for any treatment. The outcomes of treatment were very telling. As one would expect, the best outcomes was in the ***combination treatment*** arm.

Also significantly improved was the ***intensive medication*** *group*. The worst outcome was in the ***treatment as usual*** *group*. The ***psychosocial only*** *group* was better than the ***treatment as usual*** *group* but not statistically significant. In other words, the only statistically improved group over the ***treatment as usual*** *group* were those that included medication either intensively on its own **or** in *combination with psychosocial treatment*. When the specific symptom measures were reviewed, approximately 90 % of the effect was from medication effect. While this may seem to indicate that *medication only treatment* is all that is required, especially once costs are also factored in, the patients and family prefer the *combination treatment*. This suggests the likelihood of better compliance to meds with *combination treatment* in real life, which unlike in the study does not have supports to ensure medication compliance.

There have since been several longitudinal follow-ups of the MTA study indicating no sustained improvements on medication. Various explanations have been given for this. Caution however is needed in interpreting these studies given that randomization was ended at 14 months of treatment, and so any treatment or no treatment combination can occur. The key learning from these longer-term follow-ups is in the differences in family variables of the children doing well. These tend to be from intact, functional, involved, and socioeconomically successful parents (Murry et al. 2008). This suggests an approach to improve parental capacity likely

to be helpful. This trend is not unlike other areas of medicine, where better outcomes tend to occur in those with better psychosocial and socioeconomic functioning. As such, minimizing psychosocial adversity has much promise as an intervention on top of the obvious and significant gains from pharmacological treatment.

Overall the key taken away point from the MTA study is the large effect size of pharmacological treatment for ADHD over and on top of the smaller effects of psychosocial treatments (The MTA Co operative Group 1999).

Risks of Treatment

The key modality of pharmacological treatment has historically been with the psychostimulants. These have been from the various formulations of both the methylphenidate and amphetamine class of stimulants (Canadian ADHD resource alliance practice guidelines 2013). More recently, non-stimulants have also become a much larger proportion of treatment especially with the advent of atomoxetine and long-acting guanfacine. Each group has their own advantages and disadvantages. Insofar as substance use disorders go, however, the major concern is with abusability and the risk of diversion of the psychostimulants. As a result, we will review this in some detail. As for other side effects and potential adverse effects, it is beyond the scope of this review to delve into with any detail, though we will try to cover the key concerns.

As one would expect, both classes of stimulants, i.e., methylphenidate and the amphetamines, have the same possible side effects, though not necessarily in the same individual. These are typically abdominal discomfort, decreasing appetite, dry mucosal membranes, headaches, slightly increased heart rate (4–5 beats per minute) and BP (4–5 mmHg), and, if taken too late in the day for the duration of the formulation, insomnia. On many occasions, however, it is ADHD itself that confers insomnia due to chronic motor and cognitive restlessness, and not the medication. The timing of the onset of the insomnia is important to distinguish this and is important in that long-acting stimulants can actually improve sleep by decreasing restlessness, if insomnia is due to ADHD symptomatology. There have also been concerns of cardiovascular events, e.g., possible sudden death. Upon closer review, however, it appears there is no significantly increased incidence of sudden death when compared to the background rates. Nonetheless, it is the opinion of electrocardiophysiologists that the main concern is possible arrhythmia due to congenital heart disease and especially channelopathies. These are congenital conduction anomalies stemming from abnormal microchannels of conduction. The recommendation is to screen for congenital heart disease in one's history. This includes screening for the presence of:

(a) Prior congenital heart disease diagnosis
(b) Severe syncopal episodes especially due to exertion
(c) Severe exercise intolerance, e.g., unable to climb one half flight of stairs or walk down a hallway without dyspnea
(d) Family history of sudden death before age 50
(e) Severe chest pains

If present, EKG and cardiology consultation are recommended prior to medication.

This is the case for *all* ADHD meds, both stimulants and non-stimulants. Other side effects generally are acclimatized to usually in less than 1 week. If these persist, a switch to the other class of stimulant often is all that is needed to improve side effects. The stimulants have some of the highest effect sizes of medications in both medicine and psychiatry, with Cohen's effect size of approximately 0.9–1.0. Hence, even taking into account side effects, it is uncommon indeed for a patient not to benefit from or be unable to tolerate a stimulant for his or her ADHD (Arnold 2000; Faraone and Buitelaar 2010).

In the area of substance abuse, a bigger cause for concern is the diversion and abuse of medical stimulants by the substance-abusing population. This is generally not abused by the ADHD patient, but, rather, diverted by them for money to buy other substances of abuse. Fortunately this issue is easily dealt with as it is usually the short-term immediate-acting medications that are abused. This is due to their ease in being abused parenterally, usually by grinding down and snorting intranasally or by IV routes. The NIDA has noted that both cocaine and medical stimulants are abusable and can result in intoxication, especially parenterally, due to the very rapid rate of rise of concentration of stimulant with both, hence the feeling of intoxication. Interestingly, if parenteral abuse is prevented, typically by the formulation of the medical stimulant, then oral use does not result in intoxication, due to the slow rate of rise of concentration of the stimulant (Volkow and Swanson 2003; Volkow 2006). This is one of the rationale for the recent inclusion of the *long-acting* stimulants as *1st line* for the treatment of ADHD (Canadian ADHD Resource Alliance Practice Guidelines 2013).

The other is the obviously advantageous effect on compliance due to once a day dosing versus the need for multiple dosing with immediate-release formulations (Farone 2009). The methods of ensuring prolonged delivery by the long-acting stimulants are also the same mechanism that prevents its parenteral use, hence minimizing the rapid rate of rise of the stimulant in the blood needed for the feeling of intoxication.

These mechanisms include beaded formulations with some beads immediate and some delayed release in various proportions, e.g., Adderall XR (Product Monographs). The OROS technology where a laser-drilled hole is made in one end of a rigid capsule and then filled with two portions of increasing concentration of stimulants to achieve an ascending profile of serum concentration. These are propelled by a *push* compartment in the far end of the capsule consisting of a polymer that expands with water, thereby *pushing* out the stimulant at a measured and predeterminate rate, e.g., Concerta (Product Monographs). There is also the new generation transdermal system where the glue and stimulant molecules are interlaced and cannot be separated easily physically and which only allows for *1 sticky episode*, i.e., cannot be transferred once applied – Daytrana patch (Product Monographs). Finally, the most elegant is the recent development of prodrug Vyvanse technology. Here the active stimulant

molecule is covalently bonded to a lysine amino acid molecule (Product Monographs). Once this occurs there are several advantages. Firstly, the new molecule is inert and so has no metabolic activity until the covalent bond is cleaved by a red blood cell membrane-bound enzyme. Secondly, the use of lysine allows the molecule to be recognized by gut cell transporters which actively transport the molecule into the blood stream.

Thirdly, once in the blood stream, most of the molecules are able to bypass the liver due to the inert properties of the molecule. Finally, once in the systemic circulation, the prodrug is cleaved at a fixed rate-limiting step, thereby resulting in a very long duration of action, up to 13–14 h. This technology is especially useful for the substance-abusing individual in that the prodrug is very hard to abuse. Cleaving the prodrug into its constituent stimulant is a very involved and time-consuming process, making the prodrug difficult to abuse or divert. This gives the prodrug stimulant (Vyvanse) an additional margin of safety over other long-acting technologies for stimulants.

The final option is with treatment with the non-stimulant, hence non-abusable anti-ADHD medication. At present there are two molecules available, i.e., atomoxetine (Strattera) and Guanfacine XR (Intuniv) that has formal regulatory body approval for the treatment of ADHD (Product Monographs). Despite its safety profile in substance-abusing populations, non-stimulants, while very effective, has a somewhat lower, though still impressive, effect size for the treatment of ADHD (better than the effect size of SSRI for depression as comparison). As a result, we need to keep all options open and available to ensure optimal treatment and outcomes (Canadian ADHD Resource Alliance Practice Guidelines 2013). This includes psychosocial, psychological, and of course a wide choice of pharmacological treatments. One of the most potent treatments for this rather large percentage of substance-abusing adolescents is in fact family therapy (Williams and Chang 2000; Waldron and Turner 2008), where treatments including pharmacological need to be done within the context of a family structure that supports pharmacological treatment in order for this to be successful.

137.2.2 Adolescent Substance Abuse

Substance abuse and misuse is present in all cultures. What is less well appreciated is the developmental perspective of this. It is very often assumed that SUDs are an adult problem. A review of epidemiological data reveals otherwise however. In the USA the Substance Abuse and Mental Health Services Administration has kept regular data on the epidemiology of substance abuse. Tellingly, the median age of peak use occurs in young adults in the 18–20-year-old age group. This then drops off to either side of this age with a long trailing arm into the elderly, like a bell curve (Substance Abuse and Mental Health Services Administration 2009). On the leading side the beginning of the onset of substance abuse seems to begin at about age 12 when measurement begins. This has significant implications for the prevention and treatment of SUD. It is especially so if we conceive of SUD as a *childhood*

disorder that persists into adulthood. The suggestions for this are immense as for many other chronic medical conditions now understood to have pediatric beginnings.

To begin with, we need to screen for family history. It is well known that adolescent substance abusers have much higher rates than controls of other members of their family also being substance abusers (Clark et al. 1998; Kaminer 1994). Although this has often been framed as environmental modeling, as our understanding of developmental psychopathology improves, we are also coming to appreciate the heritability of the underlying psychopathology, both in substance abuse and especially in other concurrent disorders. In fact, the common comorbidity of ADHD is also the most heritable. How does having the ADHD genotype lead to the development of an SUD? What are the multifactorial risk factors that lead to SUD in the ADHD individual?

We have already discussed that nicotine use is a key major risk for ADHD individuals. It is also a key risk for their parents. As a result, there is significant environmental risk from in utero exposure, on top of the role modeling as a child and adolescent (Milberger et al. 1996; Neuman et al. 2007). Nicotine is also often used by ADHD individuals to self-medicate their own ADHD symptoms. This is so well recognized that pharmaceutical companies are already involved in looking at the use of nicotinic agonist (both complete and partial) for their potential in ADHD treatment. These molecules have not as yet resulted in a new class of ADHD treatment due primarily to side effects.

Is it any surprise then to be aware that ADHD individuals tend to start smoking tobacco earlier, smoke more, and have a harder time stopping than those without ADHD (Milberger et al. 1997; Kollins et al. 2013)? Due to the very early age of onset of nicotine abuse (Substance Abuse and Mental Health Services Administration 2009) into late childhood and preadolescent ages, the youth is further put at risk by their exposure to other tobacco-using peers, often older and more troubled. This affiliation very easily leads into invitations to a "party" where they are further exposed to many other substances of abuse. This is very attractive for an ADHD child due to the profound psychosocial deprivation secondary to the negative effects of ADHD on socialization as discussed (Strine et al. 2006). The ADHD child often has no *real* friends nor even any experience at going to a *party* as they have often never been invited to classmates' birthday parties and the like due to their perceived lack of *likability* and poor social skills (Strine et al. 2006). They therefore take to the newfound *friends*, negative as they are, like drowning individuals to life buoys. We have often observed that once substance-abusing ADHD adolescents give up their substances of abuse, they no longer have any friends as substance abuse was their only successful strategy to friendships. No wonder untreated ADHD individuals have an even harder time giving up their substance abuse than those without ADHD.

A particularly vulnerable group is the females with ADHD and SUD. This is no surprise as ADHD is present epidemiologically in approximately equal amounts in both males and females. However, males are treated more than females, as clinical populations often show a male to female ratio of 4–5:1 (The MTA Co operative Group 1999). This is due to the peculiarities of psychiatric presentations

in children. Children are identified by the adults in their lives and do not come to medical attention as a result of self-report, unlike other medical symptoms. Boys with ADHD tend to have more behavioral problems and so more frequently are identified by teachers as needing intervention. Girls are more socially savvy and less behaviorally troubled, which has led to their lower rates of clinical presentations. Once they are an adult, males and females present at the same rate, as they can self-present with their now better self-awareness of their personal problems. As discussed, untreated ADHD individuals, males or females, have a much greater risk of SUD. No wonder the higher untreated ADHD population of females now presents with SUD, one of the complications of untreated ADHD. This is a big concern, as females with SUD, especially young females, are at a much higher risk of traumas and, in particular, sexual traumas. Once traumatized, the development trajectory is often permanently altered resulting in personality and other psychiatric problems. We need to ensure that young girls with ADHD, who often act well, perform well (though well below their potential), but has significant residual ADHD symptoms with its functional and psychosocial sequelae, are identified and treated early to prevent development of complications, like SUD, which affects her to a much greater degree than males (Davis and DiNitto 1996).

Once substance abuse begins, the ADHD individual often gravitates to specific substances of abuse. These often are those that seem best at self-medicating the underlying ADHD symptoms. In our experience, as well as those in recent NIDA studies, the most commonly abused substance in the ADHD adolescent is cannabis (Riggs et al. 2011). The adolescent often informs clinical staff that the use of cannabis:

(a) Helps them to calm down
(b) Helps them to fall asleep at night
(c) In low doses seems to improve attention

These are profound insights into ADHD symptoms, since these are often the cardinal symptoms of untreated ADHD. This also makes sense neurophysiologically (Castle and Murray 2004). The active ingredient in cannabis is Δ9 tetrahydrocannabinoid (THC). This mimics an endogenous cannabinoid (anandamide) which binds at the CB 1 receptor. Interestingly, these neurons often terminate on dopaminergic neurons, postulated as the source of difficulties in ADHD. It is also the site of action of medications for the treatment of ADHD. Thus, cannabinoid abuse makes pharmacological sense in self-medication, at least initially.

Unfortunately, like other drugs of abuse, another mechanism results in difficulties over time. This is the principle of TOLERANCE. As this builds, the increased consumption then results in deteriorations in the very areas of functioning the self-medication initially improves on. With cannabis, there are also two other factors to consider. The first is the trend toward higher and higher-potency cannabis. This trend in Canada began in the 1980s. This was due to several high-profile cases of toxicity due to residual pesticides sprayed on the cannabis plant. The serious injury and deaths resulted in an attempt to *grow your own*. Unfortunately, the Canadian climate, i.e., severe cold, resulted in very high

and uncompetitive costs due to the heating and lighting costs. In a bid to compete, genetic engineering was used to increase the potency from 2 % to 3 % THC by weight, up to a maximum tested of 29 % THC by weight, i.e., compete on quality versus cost. This had two implications that are related. Firstly is the finding in several cohort studies that the earlier the onset of use in adolescents and the greater the amount of use (a given with high-potency cannabis), the higher the risk of development of psychosis (Castle and Murray 2004; Englund et al. 2013). Secondly, despite the ability to increase the amount of Δ9 THC, we have not increased appreciably the concentration of cannabidiol which has properties as an atypical antipsychotic (Englund et al. 2013). The combination of these two factors has resulted in a large increase in Canadian admissions to psychiatric inpatient and early psychosis programs with youth and young adults with first-onset psychosis. The vast majority of these patients invariably have positive urine drug abuse screens for cannabinoids at the time of admission. As if this was not enough, there are the usual well-described cannabis-induced mood and anxiety disorders that, if onset early and if poorly treated, can again change the developmental trajectory of the afflicted individual and set off into action chronic mood and anxiety disorders.

Even if the youth escapes the psychotogenic, mood, and anxiety effects of the high-potency cannabis, there is the usual psychosocial and functional deleterious effects of cannabis that often potentiate the very psychosocial and functional deleterious effects of untreated ADHD (Von Polier et al. 2012). These include the poor social skills and socialization made worse by the use of substances as a socialization tool. The substance-abusing lifestyle also increases the risk in ADHD individuals for risk taking and criminality. The withdrawal effects of cannabis, in particular irritability, worsen the often coexisting oppositional and defiant attitudes and behaviors. This reinforces the alienation from authority figures, family members, and sources of real support, for like-minded peers and the using community. These all combine to result in functional deterioration in the areas of academics and school, occupation, and premature emancipation from family and often result in homelessness and becoming esconded in a permanent underclass of crime, drugs, prison, and poverty with concomitant poor physical and mental health with real and permanent premature morbidity and even mortality.

137.2.3 Treatment

As in any medical discipline, the key to treatment begins with assessment. This is not only to make a differential diagnosis and diagnosis but also to focus on the areas of functional strength to be built onto and the areas of functional weaknesses that will require remediation. As important in an often complex interrelated environmental and genetic interaction is to intervene in many areas of need with various modalities of treatment, all of which are individualized for each particular patient and their family. Families are an extremely important site for intervention and are in fact the anchor to allow for successful integration of treatment modalities for any

adolescent. Even those without families such as those which are in custody of the state, family members still involved, and surrogate families are potent targets for intervention. The determination of how to proceed in all of these areas is only possible with optimal assessment.

137.2.3.1 Assessment

The ideal is for a concurrent disorder assessment to occur at the very start. This is due to the very high comorbidity of adolescent substance abuse with psychiatric disorders. At the same time, we do recognize that the availability of the ideal concurrent enhanced program by the definitions of the American Society of Addiction Medicine is not available in every community/treatment program regardless of whether the primary focus is on substance abuse or psychiatric disorders. Nevertheless, a very high index of suspicion needs to be present with both groups of disorders and, in particular, with the top comorbidities of ADHD ± L.D., oppositional defiant/conduct disorder, mood disorders, and anxiety disorder. The use of well-validated rating scales for these disorders is recommended if symptoms are present and has been the key innovation after years of clinical research. Many of these are in the public domain and so do not require the use of precious resources to acquire (see previous tables), and scoring has been discussed.

The other recommendation is that the assessment process be seen not only as a chance to gather information but as an engagement tool with both patients and families. Although there are many ways of doing so, we at the Addiction Centre, in Calgary, have for over two decades now involved both parents and adolescent patients concurrently for the assessment process including for the substance use history. This process seems to confront the denial and minimization by both adolescents and their families. In this situation, substance abuse is perpetuated by adolescents minimizing and denying the consequences of their use, whereas parents are very aware of the consequences but minimize and deny the extent of the adolescent's use, e.g., *all adolescents experiment and I did it at that age too*. This often blinds them to the rapid development of a SUD especially those at high risk like ADHD. It is also a very good time for education, e.g., younger siblings of the proband with ADHD often also have ADHD and are at risk of using if ADHD is not well treated or not even diagnosed. They also need to be very vigilant for any use of tobacco in the younger siblings as a risk factor to SUD. Finally, parents often are not treated or even diagnosed for their own ADHD, thereby making them a much less effective ally than they are capable of being, if parental ADHD are diagnosed and well treated.

Once the assessment is completed, it is also extremely important that all are informed of the diagnosis and a treatment plan elucidated with the patient and their families. This level of clarity is often not done in favor of offering generic *counseling* or *therapy*. Clinical trials have demonstrated the evidence base of specific therapies versus unfocused *counseling*. Having a diagnosis also holds the patients, families, and the treatment team accountable for the specific interventions and treatments needed to ensure remission of symptoms. The use of very structured written diagnosis and treatment recommendations is suggested due to the presence of parental ADHD and as a result poorer executive functioning that the structure will support. This also helps

the often blended families to communicate with each other and to increase the level of buy-in of various parents and stepparents. In fact, the buy-in of the adolescent is often less important than the buy-in and commitment of families to the successful outcome of treatment (Williams and Chang 2000; Waldron and Turner 2008).

137.2.3.2 Treatment Modalities

The most effective treatment is multimodal (The MTA Co operative Group 1999; Canadian ADHD Resource Alliance Practice Guidelines 2013). This includes family, group, individual, and pharmacotherapy with long-acting ADHD medications. The family therapy includes not only therapy but specific parent skills training. If parents have ADHD or symptoms thereof, assessment and treatment greatly improve their parenting effectiveness. Individual therapy includes the use of cognitive behavioral therapy with more recently a major increase in popularity and use of Motivation Enhancement Therapy. While it is beyond the scope of this review to go in depth into these therapies, all are enhanced by the use of contingency management, or the use of rewards for gains (Carroll et al. 2006). This is also an excellent way to work parental involvement into treatment, as they are then seen as instruments not only of consequences but of rewards thereby further improving the often severe parent-child conflict so often present. Many of these therapies can also be delivered in groups for cost-effectiveness. Unfortunately, group members need to be carefully selected to avoid the often present "contagion" effect, as the negative, acting-out, risk-taking behaviors often have more overt and acute appeal than the hard work of reordering one's life and relationships.

137.2.3.3 Pharmacological Treatment

This was an area of intense discussion and disagreement for some time. On one hand, it was felt ADHD individuals needed anti-ADHD treatment in order to develop the cognitive and follow-up behavioral skills for sobriety. The intense craving for risks and novelty, the surly oppositional and defiant stance and attitude, the impulsivity, the forgetfulness and inattention and lack of follow through, the internal restlessness, and even insomnia and poor sleep of ADHD all conspire to decrease success toward sobriety even if motivated. On the other hand, there were concerns for stimulant abuse and diversion in a substance-abusing population, the risk of medication/street drug interactions in actively abusing individuals, and even the added conflicts to take medications in an already conflicted and discord filled parent-adolescent relationship. Two schools of thought emerged through this:

(a) Concurrent treatment for ADHD and SUD from the beginning
(b) Waiting for sobriety before treatment initiated for ADHD

This was felt to be such an important need that the NIDA funded a study to look just at this issue (Riggs et al. 2011). In this study 303 adolescent participants were randomly assigned to either PBO and CBT or OROS methylphenidate and CBT for their concurrent ADHD and SUD diagnoses, respectively. In terms of efficacy, the primary measures, i.e., adolescent self-reports of both ADHD symptoms and substance abuse, did not show any difference between groups. Yet, the secondary

measures, i.e., objective measures of ADHD by parental rating scale and of substance abuse by urine drug abuse screening, both showed improvements. ADHD with decreasing ADHD R.S. PARENT'S rating scale scores and substance abuse with the number of negative urine drug abuse screens. As far as safety of this strategy goes, (a) there was no increase in medication abuse and diversion and (b) both study groups mixed medication or placebo with drugs and alcohol, but there were very few adverse interactions.

These findings were interpreted by the authors as a negative study based on the negative outcomes on the primary measures. Many of us however who work with this population very regularly make the following observations of the differences between the primary and secondary measures in this study:

(a) Most children are not capable of the insight and awareness to judge changes in ADHD symptoms with treatment. This is why most studies use observer, i.e., parents/teachers rating scales. Adults are more capable of this, with adolescents in the middle.
(b) While it is true that with a good therapeutic relationship adolescents are often very truthful around their use, in others, objective urine screenings are very important. The fact that the numbers of negative screens are different is especially important as most of the adolescents in the study used cannabis. Given the lipophilic nature of the Δ9 THC and its long half-life, this means a very significantly decreased amount of use as it takes the cannabinoid so long to clear the body to result in even one negative urine drug abuse screen.

Practically speaking, then how does one incorporate these findings into clinical practice? To begin with, engagement to treatment is very important. This includes especially the engagement of parents (Williams and Chang 2000; Waldron and Turner 2008). Most often, adolescents even when willing have difficulty following through over time. Yet this is precisely what we are needing, as both SUD and ADHD are chronic disorders requiring longer-term treatment and interventions. Together with engagement, regular urine drug abuse screening is very important to at least see some gains in SUD treatment to demonstrate at minimum some patient motivation. If these conditions are met, then integrated concurrent treatment may begin with one of the long-acting and harder to abuse and divert stimulants or alternative with non-stimulants like atomoxetine. Safety can be boosted further by informed consent as to the risk of concurrent use of street drugs and medication, as well as a strategy to have parents be in charge of giving out the medication while there is active substance abuse happening. This is in fact the recommendation in some national guidelines including our own Canadian guidelines that may be accessed in English or French via the Canadian ADD/ADHD Resource Alliance website, i.e., CADDRA.ca (Canadian ADHD Resource Alliance Practice Guidelines 2013). This website also includes the public domain rating scales for not only child and adolescent but adult ADHD. There are also scales for functioning and even history and physical forms if desired. All are available free for downloads and for members, even an A*sk the Expert* service.

137.3 Conclusion

In conclusion, ADHD and SUD are one of the most common presentations and complications of undertreated or undiagnosed and hence untreated ADHD. This being a very heritable disorder, there is often many other family members with the same condition, including parents, thereby complicating treatment and necessitating very regular family involvement. Treatment of ADHD is absolutely essential to minimize the cost of psychiatric and psychosocial comorbidity for both the patient and their families and for society. It is a significant public health issue as a result. Multimodal treatment is noted to be safe even in the presence of SUD and ongoing substance use and despite being on long-acting stimulant. Outcomes are also noted to be generally positive for both ADHD and SUD with treatment.

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Perinatal Addictions: Intrauterine Exposures

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Martha L. Velez and Lauren M. Jansson

Contents

Abstract

The use and abuse of psychoactive substances by women of childbearing age is an important public health problem. Its prevalence is high and for some substances has increased in the past decade, with resultant increases in neonatal morbidity. With advances in fields such as genetics, epigenetics, and neuroimaging as well as improved research methodologies, it has been established that in utero exposure to psychoactive substances is one of the major preventable causes of disorders of fetal and infant/child growth and neurodevelopment. The effects of these neurodevelopmental alterations can appear at any time of the individual's life and can affect a variety of domains including developmental, behavioral, cognitive, and adaptive functioning. Moreover, maternal chronic substance use can compromise the maternal neural circuitries that subserve executive functioning and the regulation of stress response and consequently the ability to appropriately parent children. Expression of the teratogenic effects

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of perinatal exposure to substances can be exacerbated by a toxic or unstable prenatal and/or postnatal environment and ameliorated by a nurturing and stable one. Health-care providers play an important role in the prevention, early detection, and intervention for perinatal addiction. This chapter will describe the effects of maternal addiction on the mother, child, and maternal/child functioning and provide recommendations for screening and therapeutic interventions for families affected by perinatal addiction.

138.1 Introduction

The use and misuse of psychoactive substances among pregnant and recently postpartum women is a cause of great concern among health professionals and policy makers. Intrauterine substance exposure affects more newborns than many other common medical conditions and is linked to a variety of adverse outcomes for the pregnancy, the fetus/child, and/or the mother (Lester and Lagasse 2010). Furthermore, addiction can compromise maternal neural circuitries regulating stress responses and behavior, affecting her ability to care for the infant (Rutherford et al. 2011) which can lead to child abuse and neglect. The physiological, behavioral, and neurodevelopmental problems associated with prenatal substance exposure can appear in the fetus, at birth, or at any age and can be transient or persist throughout life causing serious emotional and financial burdens to individuals, families, and society. The management of pregnant women with substance use disorder (PWSUD) and their children is an opportunity and a challenge for both the patients and the health providers. Their identification, assessment, and successful intervention require the knowledge of the particular needs of the mother/infant dyad in the context of their community; the consequences for failing to identify and treat these mothers and children comprehensively may bring undesirable consequences for the dyad and society in general. It is the purpose of this chapter to review the (1) overall scope of the problem, (2) challenges faced by PWSUD, (3) effects of drugs on fetal/infant brain and neurodevelopment, (4) identification of PWSUD and their children, and (5) interventions to help this population of women and children.

138.2 The Problem of Substance Use During Pregnancy

138.2.1 Magnitude of the Problem

The use and misuse of licit and illicit substances is a major cause of preventable disorders of fetal growth and neurodevelopment (Floyd et al. 2009). Concerns about these known effects should lead to increased awareness among health-care providers and communities to the problems of gestational drug use, improvements in care being delivered to at-risk populations, and reductions in the prevalence of toxic exposures during the preconceptional and prenatal periods. Despite this fact,

the incidence of neonatal morbidity associated with maternal substance use has been increasing (Patrick et al. 2012), and the danger of substance use by pregnant women remains an undiminished challenge for the perinatal care provider in the twenty-first century.

138.2.1.1 Preconceptional Period

In the United States, 55 % of childbearing-age women report alcohol use, with 24.5 % reporting binge drinking in the past month (SAHMSA 2012). Women who binge drink in the preconception period are more likely than non-binge drinkers to continue drinking, even after becoming pregnant (Naimi et al. 2003). The use of tobacco among nonpregnant women aged 15–44 is 25.4 % and the use of illicit drugs is 10.8 % (SAHMSA 2012). Although pregnancy is a motivation for many women to stop drug use and to limit or cease smoking or drinking, approximately half of the pregnancies in the United States are unplanned (Henshaw 1998) and unrecognized for weeks or months after conception, putting the fetus at risk during the vulnerable period of early brain development.

In contrast to the attention dedicated to the influence of maternal factors on pregnancy outcome, the role of paternal factors on the developing fetus remains under-researched. The few epidemiological and animal studies that have explored these factors support the idea that paternal substance abuse may have a negative impact on development and that this impact could be caused by chronic substance use prior to conception (Abel 2004). Paternal alcohol use has been found to have influence on infant birth weight, congenital malformations, and cognitive functioning (Ramsay 2010). Paternal smoking has been associated with fetal growth retardation (Davis 1991). Preliminary studies suggest that paternal preconceptional substance abuse can produce heritable changes in genomic expression and phenotype in offspring via epigenetic transmission. However, the mechanisms underlying the role of the paternal substance use on physical and developmental outcomes of the offspring is unclear.

138.2.1.2 Prenatal Period

Tobacco, ethanol, marijuana, cocaine, amphetamines, opioids, and benzodiazepines are the most commonly abused substances, and polysubstance abuse is more common than monosubstance abuse. The prevalence of disorders related to prenatal substance exposure varies by ethnicity, geographic location, and population factors. Among pregnant women in the United States, it is estimated that between 16 % and 30 % smoke tobacco and 7.6–15 % use alcohol regularly with binge alcohol drinking reported in 2.6 %. Five percent of pregnant women report current illicit drug use (Lamy and Thibaut 2010; SAHMSA 2012). Adolescents are a particular concern; in 2010–2011, among young pregnant women between 15 and 17 years, the rate of illicit drug use was 20.9 % and smoking rates are higher in pregnant vs. nonpregnant teens in this group.

Despite its classification as legal in certain areas, marijuana continues to be the most commonly used illegal substance among pregnant women in the United States, with use in the last month figures ranging from 3.6 % in the general

population (SAMHSA 2005) to 23–30 % in urban samples (Fried 2011). This high consumption of cannabis during pregnancy may result from a generalized opinion that marijuana is relatively harmless. However, cannabis use during pregnancy has known harmful effects on the offspring (Campolongo et al. 2009). Between 0.5 % and 3 % of pregnant women use cocaine (Lamy and Thibaut 2010; SAMHSA 2005), and in recent years there has been a marked increase in the use of opioid analgesics in the United States, with prevalence among pregnant women in some communities of up to 17 % based on tests of neonatal meconium (Moller et al. 2010). During the last decade the overprescription, diversion, and misuse of prescription opioid medications have become a major public health burden for maternal and child health (Kellogg et al. 2011). Such an increase is especially concerning because 55–94 % of newborns exposed to opioids prenatally develop neonatal abstinence syndrome (NAS), which can predispose the infant to prolonged hospitalization, significant morbidity, and protracted developmental concerns, all of which are costly to the child, the family, and the health-care system.

138.2.1.3 Postnatal Period

Resumption of substance use following delivery is an additional concern; it has been reported that cigarette, alcohol, binge alcohol, and marijuana use rates were higher in women with a child younger than 3 months of age (20.4 %, 31.9 %, 10.0 %, and 3.8 %, respectively) compared with rates of use in the third trimester of pregnancy (13.9 %, 6.2 %, 1.0 %, and 1.4 %, respectively) (SAHMSA 2007).

138.2.1.4 Children of PWSUD

Although the exact prevalence of individuals affected by prenatal substance exposure is impossible to estimate, there is some data regarding negative consequences of prenatal substance exposure that illustrates the magnitude of the problem. Prenatal smoking is one of the most common preventable causes of infant morbidity and mortality and is associated with 30 % of small-for-gestational-age infants, 10 % of preterm births, and 5 % of infant deaths (CDC 2009). Maternal tobacco use during pregnancy doubles the likelihood of sudden infant death syndrome (Salihu and Wilson 2007). A recent report cites the tripling in the incidence of NAS in the United States between 2000 and 2009 (Patrick et al. 2012). Fetal alcohol spectrum disorders (FASD) are estimated to occur in 1 % of births (Sampson et al. 1997), although some suggest that the rate is much higher. Reporting figures for fetal alcohol syndrome (FAS) range from 0.5 to 2 cases per 1,000 in the United States (Abel 1995; May and Gossage 2001); the risk of FAS is higher in disadvantaged groups (e.g., Native Americans) in the United States with rates of 3–5 FAS affected children per 1,000 live births and up to 68.0–89.2 per 1,000 in the wine-producing regions of South Africa (May et al. 2007).

138.2.1.5 Financial Burden Imposed by Prenatal Substance Exposure

The financial burden of the problems related to maternal substance abuse during pregnancy is multifactorial. For mothers, medical costs are substantial but can be decreased by providing assessment and intervention (Goler et al. 2012). Mean

hospital charges for newborns affected with NAS increased from $39,400 to $53,400 between 2000 and 2009 (Patrick et al. 2012). Studies in the United States and Canada have indicated that the increase in cost of neonatal care for infants born to a cigarette-smoking mother is approximately $700 and the increase in cost for those exposed to cocaine is $5,110 per patient (Chiu et al. 1990; Hutson 2006). The lifetime cost of the care of individuals with FASD is approximately $2 million to $2.8 million across the United States and Canada (Lupton et al. 2004; Thanh and Jonsson 2009). A study by Credé et al. (2011) reported that in the Western Cape (South Africa), $70, 960,053 are spent annually on managing health-care needs of children with fetal alcohol syndrome/partial fetal alcohol syndrome.

138.2.2 Problems Faced by the PWSUD

The neurobiology of addiction and maternal behaviors indicates that the chronic use of drugs by women can lead to morphological and functional changes in the brain that produce a compulsive craving and drug seeking that impairs the woman's daily functioning and may affect mother/infant interaction. Addiction has been conceptualized as a dysregulation of the balance between reward systems and stress response. These two systems need to be organized and regulated to support the demands of adequate parenting practices, self-care, and decision making. Chronic use of drugs has been associated with impairment of memory and attention, executive function and inhibitory control, interoception, and self-awareness (Volkow 2005). Compromise of these functions in a pregnant/postpartum woman may explain how addiction leads to relapse and other unhealthy behaviors that affect the mother's ability to take care of herself, the pregnancy, and the infant. In the addicted mother, substance-induced brain changes can result in heightened stress reactivity as opposed to reward salience to parent–infant interaction, which may amplify negative affect state and increase drug seeking and neglectful parenting behavior, which may in turn lead to child abuse or neglect (Rutherford et al. 2011).

Addiction during pregnancy has been associated with perinatal complications related to the direct effects of the drugs or, secondarily, due to the lifestyle associated with compulsive drug use and seeking, all of which can negatively impact both the health of the mother and the pregnancy. Medical and obstetrical complications include miscarriage, premature rupture of membranes and preterm delivery, placental abruption, intrauterine growth restriction, chorioamnionitis, stillbirth, hypertension, and increased rate of infectious illnesses. Injection of drugs carries the risk of cellulitis and abscess formation, sepsis, endocarditis, hepatitis B, hepatitis C, and human immunodeficiency virus (HIV) infection. Sexually transmitted diseases are not uncommon due to unsafe sex and prostitution (Jansson et al. 1996). Poor decision-making skills can lead to risky sex, violence exposure, high levels of stress, and homelessness. Many pregnant women with substance use disorders seek prenatal care late or not at all even if they have chronic medical problems (e.g., asthma, diabetes, hypertension, seizure disorders) that increase the risk of poor perinatal outcomes. Dental problems are very common due to poor dental hygiene and inadequate nutrition.

A significant proportion of PWSUD have one or more psychiatric diagnoses (Fitzsimons et al. 2007; Wouldes et al. 2013), with this incidence ranging from 45 % to 75 %, depending on the sample. Personality disorders are also common. Psychiatric comorbidity during pregnancy has been associated with delayed prenatal care and unhealthy behaviors such as smoking, poor nutrition, and poor compliance with medical recommendations. Unaddressed maternal psychological symptoms may lead to difficulty managing emotions and stress that can contribute to communication/dyadic interaction problems after delivery and dysregulation of the newborn, making postpartum adaptation difficult for the dyad. Postpartum depression is prevalent among women receiving substance abuse treatment (Holbrook and Kaltenbach 2012). Of particular concern is the evidence that links maternal psychopathology, substance use disorders, and other psychosocial problems with negative parenting behaviors and poor developmental outcomes for children (Wan and Green 2009).

PWSUD very often have a history of traumatic experiences. A past and/or current history of abuse (physical, sexual, or emotional), neglect, abandonment, and family violence are common conditions (Velez et al. 2006). Many women grow up in multigenerational drug-using families, families with significant mental health problems, or environments where chaos, inconsistency, mistrust, and aggression are the norm. All of these situations have a significant impact on how women perceive their pregnancy, the fetus, and the child and contribute to high levels of stress. The perceptual, cognitive, and emotional capabilities of the mother and her parenting skills are built upon the scaffolding provided by her earlier life experiences. In PWSUD, this frequently leads to maladaptive and recurring unhealthy behaviors which originate as a consequence of those traumatic experiences. These maladaptive behaviors can have a negative impact on their general functioning and the well-being of their pregnancy. Inability to appropriately manage stress can lead to increased drug use or relapse to active drug use, violence, and deleterious prenatal practices that increase risks for the mother, her pregnancy, and the developing fetus.

138.2.3 The Effects of Drugs on Fetal/Infant Brain and Neurodevelopment

Negative effects of substance use during pregnancy on the fetus have been presumed since ancient times, with biblical texts and ancient Greek and Roman warnings about infant effects of maternal alcohol use during pregnancy. First described by Paul Lemoine et al. (1968), fetal alcohol syndrome (FAS) was defined as a cluster of serious physical and neurological problems due to prenatal exposure to alcohol in 1973 (Jones and Smith 1973). Beginning in the 1960s, clinicians and researchers described the effects of opioids on neonates exposed to heroin or methadone and defined criteria for identifying and treating infants with “narcotic neonatal abstinence syndrome” (Rosenthal et al. 1964). Teratologic theories of prenatal harm due to individual substances used or abused by pregnant women as the cause of problems encountered in children of PWSD continued into the 1980s.

During the cocaine epidemic in the United States, several studies based on case reports or small samples created the prejudiced portrayal of "crack children" as a harbinger of profound negative effects on the educational, legal, and medical systems (Toufexis 1991). The media attention generated by these reports gave origin to several well-designed, longitudinal studies controlling for environmental and social issues that could influence the neurobiological effects of drug exposure during development. Results of studies carried out in the 1990s indicated that the consequences of prenatal drug exposure on the fetus and child are multifactorial and complex and should be attributed not only to direct effects of the drug on fetal development but to the interaction between genetic, epigenetic, and environmental factors before and after birth (Bandstra et al. 2010; Salisbury et al. 2009).

Most psychoactive substances taken by pregnant women cross the placenta, have a longer half-life in the fetus than in adults, and have higher concentrations in fetal blood than in maternal blood (Finnegan et al. 1992). The psychoactive substance may affect biologic functions either through the binding of the active components of the drug's receptors in the central nervous system or by affecting the release and reuptake of neurotransmitters. Neurotransmitters and neuromodulators appear early during embryogenesis and their signaling serves key functions during neurodevelopment; they are involved in the control of neurodevelopmental processes such as neurogenesis, neural progenitor proliferation, lineage segregation, and the migration and phenotypic specification of immature neurons. Alterations in these processes can change neurodevelopmental trajectories via a variety of actions depending on the substance, the timing of exposure, and the system affected. As an example, prenatal alcohol exposure may disrupt neural development by interfering with myelination, synaptogenesis, and cell migration and by enhancing cell death (Bonthius and West 1991; Chen et al. 1999; Miller et al. 2006; Maier and West 2001). Developmental effects secondary to disruptions in brain development may not become clinically apparent until later in life and may be produced in the fetus at dose levels that are relatively harmless for adults (Frederick and Stanwood 2009; Thompson et al. 2009).

The foundations of brain architecture and function are established early in pregnancy through dynamic interactions between genetic influences and the prenatal environment and experiences (Shonkoff 2012). Though it was previously believed that genetic mechanisms are unchallengeable, expression of early gene networks can be disturbed not only by maladaptive genetic mutations that disrupt important regulatory genes but also by prenatal environmental influences, such as drugs, alcohol, toxins, and inflammatory responses. The effects of the drugs depend on factors such as fetal developmental stage of exposure (critical periods), drug type, dose and use patterns, use of more than one substance, as well as other uterine stressors that are frequently seen in women with addictions. Prenatal substance abuse often occurs in the context of risk factors such as maternal psychiatric comorbidities, toxic stress, exposure to violence, homelessness, poor nutrition, sporadic or absent prenatal and medical care, and lack of social support which can alter the prenatal environment independently of drug exposures per se. Postnatal factors such as nutrition, socioeconomic conditions, parenting practices, and exposure to early adversity can also alter gene expression and modify the processes of brain development in the infant.

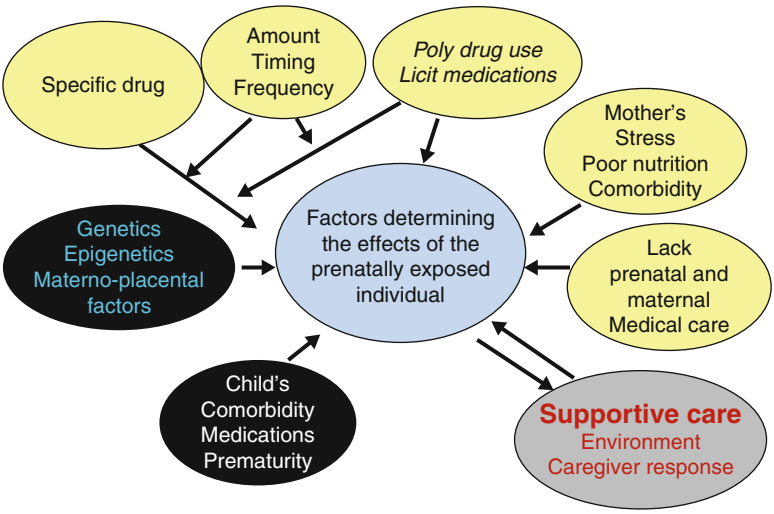

Fig. 138.1 Factors determining the effects of the prenatally exposed individual. These include maternal factors (drug use, medical care, stress), infant factors (including NAS and comorbid pediatric conditions such as preterm birth), and genetic/epigenetic and placental factors

The environment encountered in fetal and neonatal life exerts a profound influence on physiological function and risk of disease in adult life, and multiple risk and protective factors have been investigated for their roles as mediators or moderators of the effects of maternal drug use on the developing child. Recent advances have identified specific genes that appear protective for the development of NAS in opioid-exposed infants (Wachman et al. 2013). In contrast, adverse prenatal environments, including those created by prenatal substance exposure, may result in epigenetic modifications, altered hypothalamic–pituitary–adrenal (HPA) axis activity, and elevated corticosteroid levels in the mother and fetus. These changes, which have been found to occur with cocaine and alcohol (Weinberg et al. 2008; Salisbury et al. 2009; Hellemans et al. 2010), may alter the programming of the fetal neuroendocrine environment, causing the fetus to "reset" or adapt his/her biologic functioning and predispose the child to having an altered expression of key candidate genes leading to problems with behavioral and emotional dysregulation that can impact physical and mental health and developmental trajectory (Lester and Padbury 2009; Lester and Lagasse 2010). Regardless of mechanisms of harm and confounding by other risk factors, it is accepted that children exposed to substances during pregnancy are at increased risk for a variety of conditions that portend future neurodevelopmental and other difficulties. These effects can be seen during the neonatal period or at later stages of development. It is easy to comprehend the wide variation in infant outcome in substance-exposed pregnancies with the myriad factors at play in these pregnancies (Fig. 138.1).

138.2.3.1 Neonatal Period

Neonates exposed to substances during pregnancy are at increased risk for a variety of conditions that can make adaptation to extrauterine life a challenge for the neonate and his/her caregivers and can negatively alter mother/infant interaction and/or the trajectory of development if not recognized and properly treated. The following are the most widely recognized clinical conditions associated with in utero substance exposure during the neonatal period.

Substance-Related Adverse Birth Outcomes

Almost all drugs of abuse have been associated with drug-related adverse outcomes such as preterm birth (e.g., nicotine, alcohol, cocaine, benzodiazepines), low birth weight, and intrauterine growth restriction (e.g., nicotine, alcohol, cocaine, methamphetamine) (Wikner et al. 2007; Plessinger 1998). Many substances used by PWSUD can shorten gestation and impair fetal growth without resulting in preterm deliveries or LBW, as traditionally defined. Small-for-gestational age rather than preterm birth is the main mechanism through which smoking causes excess infant mortality. Epidemiological studies have associated low birth weight with insulin resistance, hypertension, coronary artery disease, and non-insulin-dependent diabetes in later life. A suggested explanation for this association is intrauterine programming in response to alteration in the maternal placenta–fetus unit (Barker 1995). Some studies suggest that about 5 % of infant deaths in the United States are attributable to maternal smoking while pregnant, with variations by race/ethnicity (Salihu and Wilson 2007). Additionally, substance-exposed infants are at higher risk than the general population for maloutcomes due to maternal sexually transmitted diseases or other infections such as TORCH and HIV infections.

Neonatal Abstinence Syndrome (NAS)

Neonatal withdrawal is a group of signs and neurobehaviors experienced by the infant that occur after discontinuation of gestational exposure to psychoactive substances taken by the mother. The symptoms associated with NAS include high-pitched cry/irritability, sleep–wake disturbances, alterations in infant tone and movement (hyperactive primitive reflexes, hypertonicity, and tremors with resultant skin excoriations), feeding difficulties, gastrointestinal disturbances (vomiting and loose stools), autonomic dysfunction (sweating, sneezing, fever, nasal stuffiness, and yawning), and failure to thrive. Opioid-induced NAS symptoms usually begin during the first 4 days of life with the clinical signs escalating over time as the drug is metabolized and eliminated by the newborn. NAS is variable in its presentation in severity of infant display, amount and types of symptoms presented, and onset of symptoms. The Finnegan scoring system was developed as a clinical tool to measure withdrawal in newborns exposed to opiates (Finnegan 1975).

Although the Finnegan scoring system was developed to evaluate symptoms of withdrawal among opioid-exposed infants, this scale has been used in children exposed to other substances. Neonatal withdrawal signs have been reported when

using the Finnegan score in infants exposed to benzodiazepines and alcohol and heavily nicotine-exposed neonates (Godding et al. 2004; Pichini and Garcia-Algar 2006; Coles et al. 1984). Signs of benzodiazepine withdrawal include hypoventilation, irritability, hypertonicity, and "floppy infant syndrome," particularly after use in late gestation. These symptoms can appear within a few days to 3 weeks after birth and can last for several months. A neonatal alcohol withdrawal phenomenon has been described in children born to alcoholic mothers and includes jitteriness, irritability, seizures, opisthotonus, abdominal distention, excessive mouthing movements, and reflex abnormalities (Pierog et al. 1977; Robe et al. 1981). A NAS has been described and disputed for PCP-, cocaine-, and methamphetamine-exposed infants (Behnke and Smith 2013).

Most children exposed to opioids undergo NAS. However, only a portion will require medication for more severe presentations and symptoms that impair adequate functioning of the baby in the areas of feeding, sleeping, growth, and interaction. Evaluation of the infant to determine the need for NAS pharmacotherapy and determination of dosage of medication is usually done using the Finnegan scoring system or a variant of it (Jansson et al. 2009). Opioid medications, such as morphine sulfate and methadone, are recommended for the treatment of opioid-induced (i.e., exposure to heroin, morphine, methadone, prescription opioids, and buprenorphine) NAS (Hudak and Tan 2012). The infant's display of NAS can profoundly affect maternal functioning due to feelings of guilt and subsequently her interactions with the newborn, further compounding the threat to the problematic mother/dyad interaction and the resultant developmental trajectory of the newborn. Non-pharmacologic care (i.e., comforting techniques, modification of environment according to the newborn's needs, education to the parents) should be used with all newborns to support their functioning and development and prevent disruptions in the mother/infant dyad (Velez and Jansson 2008).

Neurobehavioral and Regulatory Problems

Each newborn has a particular repertoire of physiological and behavioral characteristics that depend on the maturation, organization, and regulation of different interactive systems: state control and attention, sensory integration, motor/tone performance, and autonomic control (Als 1982). The direct and/or indirect effects of drugs in the fetus can negatively impact the newborn's functioning in one or more of these domains affecting the newborn's neurobehavioral display and capacity for interaction in an individualized way. These regulatory difficulties experienced by the neonates that are not directly attributed to NAS have been studied for various substances using the Neonatal Behavioral Assessment Scale (NBAS) (Brazelton 1973) or the NICU Network Neurobehavioral Scale (NNNS) (Lester and Tronick 2001). These scales, developed as neurobehavioral assessment tools for normal and at-risk infants, respectively, have been used to evaluate how stressors, such as in utero substance exposure, affect infant self-organizing neurobehavioral capacities and to describe the neurobehavioral effects of in utero exposure to cocaine (Lester et al. 2002), nicotine (Law et al. 2003), marijuana (de Moraes Barros et al. 2006), alcohol (Chiriboga 2003), methamphetamine

(Smith et al. 2008), and methadone (Velez et al. 2009). Using the NNNS, cocaine exposure was associated with lower arousal, poorer quality of movement and self-regulation, higher excitability, hypertonia, and nonoptimal reflexes, with most effects maintained after adjustment for covariates (Lester et al. 2002). Neurobehavioral symptoms described in neonates exposed to nicotine include impairment of arousal, irritability and hyperexcitability, hypertonicity, and signs of stress/abstinence (Law et al. 2003). Neurobehavioral effects of in utero cannabis exposure range from mild deficits in visual functioning, heightened tremors, startling, jitteriness, hypotonia, and lethargy to difficulties with arousal, regulation, and excitability (Fried 1991; de Moraes Barros et al. 2006). Neurobehavioral signs associated to phencyclidine (PCP) after delivery consist of decreased attention, high-pitched cry, poor visual tracking, coarse flapping tremors, lethargy, nystagmus/roving eye movements, poor feeding, and altered newborn reflexes (Strauss et al. 1981; Golden et al. 1987). Poor habituation, low levels of arousal, and motor abnormalities have been identified in infants of heavy alcohol drinking women (Chiriboga 2003). Prenatal methamphetamine exposure has been associated with decreased arousal, increased stress, and poor quality of movement (Smith et al. 2008).

Congenital Malformations

Aside from alcohol, which has a clearly defined pattern of birth defects, studies evaluating the correlation between congenital anomalies and periconceptional drug use generally find inconsistent or no associations (Evans et al. 1979; van Gelder et al. 2009). While a few case reports, retrospective studies, and studies with small samples describe associations of some drugs with particular anomalies, large-scale and prospective studies do not generally confirm these associations (Behnke et al. 2001, 2013). A systematic literature review of studies carried out between 1959 and 2010 found a significant positive association between maternal prenatal smoking and congenital malformations including cardiovascular/heart defects, musculoskeletal defects, limb reduction defects, missing/extra digits, clubfoot, craniosynostosis, facial defects, eye defects, orofacial clefts, gastrointestinal defects, and undescended testicles (Hackshaw et al. 2011). However, these associations have not been found by others (Evans et al. 1979). Minor physical anomalies such as true ocular hypertelorism and severe epicanthus have been reported in heavy users of cannabis (O'Connell and Fried 1984), but there is a lack of a definitive convincing relationship between physical anomalies and prenatal cannabis exposure in general (Astley et al. 1992). Congenital anomalies had been reported in cocaine-exposed infants, but larger recent studies have not documented those associations (Behnke et al. 2001). Infants exposed in utero to phencyclidine (PCP) have been reported to display dysmorphologic features that consist of microcephaly (Strauss et al. 1981) and alterations in facial features (Golden et al. 1980). Isolated cases of cardiac defects, cleft lip, and biliary atresia have been reported in neonates exposed to methamphetamine (Plessinger 1998), but these findings have not been found in other samples (Little et al. 1988). There has been inconstant reporting on the relative risk of congenital anomalies (orofacial clefts) among infants exposed to benzodiazepines (Dolovich et al. 1998; Iqbal et al. 2002).

Malformations associated with alcohol abuse include the dysmorphic facial features seen in fetal alcohol syndrome (FAS) or partial fetal alcohol syndrome (pFAS) (short palpebral fissures, smooth philtrum, and thin vermillion border) and the congenital malformations seen in the alcohol-related birth defects (ARBD) (cardiac defects, eyesight and hearing issues, urinary problems, joint abnormalities, and skeletal problems) (Jones and Smith1973; Stratton et al. 1996). Reports from autopsies of infants with FAS and human imaging studies demonstrate abnormalities in overall brain size and shape particularly in the cerebellum, basal ganglia, and corpus callosum (Clarren 1977; Mattson and Riley1996; Lebel et al. 2011).

138.2.3.2 Problems Related to Individual Substance Exposures

Illicit drugs and licit drugs that are misused are considered neuroteratogens that can compromise critical neural pathways in the developing brain. Although the number and severity of negative effects of alcohol and drugs can range from subtle to serious, they can be lifelong.

Alcohol

Alcohol is generally acknowledged as the leading human teratogen and is the top known cause of preventable neurodevelopmental disorders in Western society (Abel and Sokol 1991; Caetano et al. 2006). The effects of prenatal alcohol exposure vary depending upon timing of exposure, blood alcohol concentration, and patterns of maternal use. Although a dose-related severity of effects has been found, there are no evidence-based studies to suggest that any particular amount of alcohol use is safe during pregnancy. Furthermore, only a percentage (perhaps only 5 %) of women classified as "heavy drinkers" during pregnancy give birth to children who meet diagnostic criteria of FAS (Abel 1995). However, which children will be affected by maternal alcohol use is not predictable, so women should be advised to abstain from drinking during pregnancy or while attempting to conceive.

Alcohol-induced effects on pregnancy and the fetus/infant include prenatal loss, fetal growth retardation, congenital malformations, and neurodevelopmental problems. The different categories of effects related to prenatal alcohol exposure are grouped under the nondiagnostic umbrella term fetal alcohol spectrum disorders (FASD). Four different groups of symptoms constitute FASD: fetal alcohol syndrome (FAS), partial FAS (pFAS), alcohol-related birth defects (ARBD), and alcohol-related neurodevelopmental disorder (ARND).

Fetal alcohol syndrome is characterized by a combination of (1) a specific facial phenotype (short palpebral fissures, a thin upper vermillion, and a poorly formed philtrum), (2) prenatal and/or postnatal growth deficiency (prenatal and/or postnatal height and/or weight at or below the tenth percentile for age), and (3) a range of neurostructural and/or neurodevelopmental defects (Jones and Smith 1973; Hoyme et al. 2005; Astley 2006). Prenatal alcohol exposure may or may not be confirmed in FAS.

Partial fetal alcohol syndrome (pFAS) refers to a less severe FASD in which a child presents with less than three characteristic facial dysmorphic features and

fewer abnormalities in growth or central nervous system structure and function than a child with FAS (Hoyme et al. 2005). Children with pFAS have a confirmed history of prenatal exposure to significant amounts of alcohol but do not meet all of the criteria to qualify for the FAS diagnosis.

Alcohol-related birth defects (ARBD) is a term referring more specifically to physical anomalies associated with prenatal alcohol exposure including malformations and dysplasia (e.g., dysplastic kidneys, ptosis, atrial and ventricular septal defects, neurosensory loss) (Stratton et al. 1996; Jones et al. 2013). Confirmation of prenatal alcohol exposure is required.

Children with *alcohol-related neurodevelopmental disorder* (ARND) have a confirmed maternal history of use of alcohol during pregnancy and normal growth, lack the facial features seen in FAS, and display a pattern of behavioral, developmental, and/or cognitive problems that are inconsistent with the developmental level of the individual. The neurodevelopmental problems cannot be explained by the genetic contribution of the biologic parents or abnormalities in brain maturation related to toxic environmental factors. Neonates affected by ARND can be challenging to care for, due to regulatory problems causing irritability, disordered sleep, and feeding problems (Coles et al. 1984). Infants may have deficits in language and motor skills and attention and impulse control deficits during the toddler and preschool years (Kable and Coles 2004). At school age they can have learning disabilities, social skills deficits, attention and memory problems, and sensory integration disorders (Streissguth et al. 1990). Deficits in attention and arithmetic skills seem to be especially marked and persistent. There are many studies documenting cognitive deficits and behavioral–emotional difficulties in children with FASD (Kodituwakku 2007; Riley and McGee 2005). Deficient adaptive behaviors, with social deficits becoming pronounced as they grow older, have been described. If early detection and intervention for these problems are not provided, secondary disabilities may arise during adolescence and adult life. In affected adults, the implications and effects of the disabilities may involve troubles with the law, mental health problems, inappropriate sexual behaviors, alcohol and drug problems, and problems with employment and dependent living (Streissguth et al. 1996). However, while FASD is a leading and preventable cause of mental retardation, not all people with FASD have cognitive limitations. This fact has important implications, because alcohol-exposed individuals with IQ scores of $\geq$70 (i.e., those not defined as mentally retarded according to current standards) may not qualify for supportive services, despite evidence that these individuals perform poorly on tests of complex attention, verbal learning, and executive functioning. Adaptive functioning is also affected in this population and many individuals identified as having FASD are unable to live or work independently. Therefore, general cognitive ability alone may not be an effective indicator of special service needs in the FASD population.

The magnitude of the health burden (Lupton et al. 2004) combined with the unchanging incidence of FASD, despite efforts to educate the public about the risk of alcohol use during pregnancy, make the early diagnosis of and intervention for maternal alcohol abuse in an effort to prevent damage to the developing brain a high research and public health priority.

Nicotine

Smoking during pregnancy is harmful for the mother and child, with increased risk of prenatal complications such as abruption, placenta previa, perinatal mortality, impaired fetal growth, higher neonatal stress and irritability, neonatal hearing loss, and respiratory problems (Cornelius and Day 2000). Prenatal nicotine exposure has been associated with neurobehavioral deficits manifested as irritability and difficult temperament during infancy and poor self-regulation during childhood. Externalizing behavior problems (Wakschlag et al. 2006) and difficulties in self-regulation, such as aggressive behavior and a higher risk of smoking in later childhood and adolescence (Goldschmidt et al. 2012), have been consistently associated with prenatal nicotine exposure.

Marijuana

Due to improved greenhouse technologies for the growth of cannabis, concentration in marijuana and hashish of delta-9-tetrahydrocannabinol (THC) – the main psychoactive ingredient of marijuana – has significantly increased during the past decades. Cannabis is the world's third most popular recreational drug used during pregnancy after alcohol and tobacco, and it is the most frequently used illegal substance during pregnancy in the Western world (SAHMSA 2009). Despite its popular use, there are few studies exploring the long-term effects of THC on the developing brain. Recent research has found that the endocannabinoid system plays a key role in prenatal and postnatal brain development, and its activation by exogenous agonists may cause alterations in the brain development that can have long-term neurofunctional alterations (Fried and Smith 2001; Campolongo et al. 2009). In utero THC-exposed infants exhibit an exaggerated startle response, tremors, sleep disturbances, poor habituation to visual stimuli, and irritability in neonates (Fried and Makin 1987). During the preschool years, deficits in verbal reasoning and short-term memory have been reported (Day et al. 1994). Adolescents that were prenatally exposed to THC may have impaired executive functioning in two domains: (1) problem-solving tasks that require complex visuoperceptual integration and (2) attention/impulsivity (Fried et al. 2003).

Cocaine

There is a large body of literature describing the effects of cocaine exposure in the developing child. During the neonatal period, cocaine-exposed neonates display signs of altered neurobehavioral regulation including state lability, altered sleep patterns, deficits in orienting and attention, and increased irritability (Chasnoff et al. 1989). Beyond the neonatal period, deficits in arousal regulation during cognitive tasks (Mayes 2002), greater reactivity, and reduced ability to modulate emotional and physiological responses to environmental stimulation during challenging tasks have been noted in cocaine-exposed infants. Other studies have reported behavior problems (Bada et. al. 2007; Bendersky et al. 2006), language (Beeghly et al. 2006), cognition (including poor sustained attention), and motor function problems. Some studies associate prenatal exposure and psychopathology (ADHD and oppositional defiance disorder) as well as substance use (Delaney-Black et al. 2011) in cocaine-exposed offspring.

Benzodiazepines

One of the most frequently prescribed class of drugs during pregnancy, despite the absence of complete knowledge of their potential adverse effects, benzodiazepines also are commonly abused licit drugs, and exposure often is unrecognized or ignored due to inconsistent screening policies. Studies evaluating the neurodevelopmental effects on exposed children have yielded mixed results, with some reporting delayed motor development and neuropsychological symptoms (Gentile 2010).

Methamphetamine

Methamphetamine is a popular illicit drug used recreationally worldwide, particularly among young adults in the United States, Europe, and Australia as part of the dance club culture. There is a limited amount of research regarding the long-term effects of methamphetamine exposure in utero (Lester and Lagasse 2010). However, there is a growing evidence from ongoing longitudinal studies that children at 3 and 5 years of age display more behavioral and emotional problems, including emotional reactivity, anxiety, depression, and social withdrawal. Five-year-old children had more attention–hyperactivity and externalizing behaviors (Lagasse et al. 2012).

Opioids

Long-term studies of children exposed to opioids are scarce, and most lack adequate control groups and have small sample sizes which preclude statistical adjustment for confounding variables, are cross-sectional, and evaluate global functions. Hyperactivity and short attention span have been noted in toddlers prenatally exposed to opiates (Rosen and Johnson 1985), and preschool children exposed to heroin demonstrated memory and perceptual problems (Wilson et al. 1979). There is no consensus from available studies about the effects of opioids on cognition. Some studies showed associations between exposure to methadone (Hans 1996) and heroin (Orney et al. 2001) and ADHD.

138.2.4 Identification of PWSUD and Their Children

138.2.4.1 Identification of Women with SUD

There is general agreement that the universal use of screening tools for alcohol/drug use among women of childbearing age will significantly decrease the incidence of problems related to substance exposure. This population of women are stigmatized by society and are perceived (and often view themselves) as having deviated from the traditional societal norms expected of women in their suitability as mothers and caregivers (Beckman and Amaro 1986; Toner et al. 2008). Women often have difficulty acknowledging their problems with substance use, and professionals are reluctant to ask women about drug and alcohol use. Health-care providers may be explicitly or passively judgmental toward the woman causing her to be unreceptive to needed health care. Therefore, women of childbearing age often enter the health-care provider/patient relationship with a feeling of shame and distrust. Such fears

are often justified in the United States, because many states have punitive laws in place for pregnant women who use drugs. Such policies often contribute to patient unwillingness to admit substance use and missed opportunities for education, support, and intervention. The result is that such women are likely to continue to use alcohol and drugs for the remainder of their pregnancy, arriving at labor and delivery unregistered, with an increased risk of adverse maternal and infant consequences (Svikis and Reid-Quiñones 2003). Even when they do seek treatment, women face practical and financial barriers to access treatment that is gender specific.

138.2.4.2 Identification of Women at Risk for SUD During Preconception

Despite a steady increase in the incidence and problems related to in utero substance exposure, use of substances during pregnancy remains underdiagnosed. Therefore, the preconception period is an important time to identify women at risk. Improving preconception health and health care can improve pregnancy outcomes by improving the overall health of women. A high proportion of pregnancies are unintended (86 % in one study of postpartum women in substance abuse treatment program), and WSUD frequently have menstrual irregularities and chaotic lifestyles making pregnancy detection difficult (Elko and Jansson 2011). In addition, conception frequently occurs during times of active alcohol/drug use/abuse, and use can continue during the early and critical stages of fetal development. Therefore, increasing universal screening and counseling during the preconception period is an important aim to improve perinatal outcomes and prevent neurodevelopmental problems. There are essentially two methods of screening for substance use disorders that can be used during the preconception and prenatal periods: maternal interview/report and biologic specimens.

Maternal Interview Screening

The US Preventive Services Task Force, the American College of Obstetrics and Gynecology, and the American Academy of Pediatrics recommend that universal screening for substance use become a routine at any preconception, prenatal, or any encounter with sexually active women and men of childbearing age. All pregnant women, regardless of socioeconomic status and/or any perceived risk, should be asked about past and current licit and illicit substance use. Maternal self-report has been commonly used but has been found to be unsatisfactory to detect exposure when compared to biologic markers. A high index of suspicion and sensitivity for substance use combined with an open-ended, nonjudgmental, and repeated questioning of pregnant women is therefore necessary to reduce reluctance to admission to use. There are several structured questionnaires that can be used. Tools that have been used in pregnant women include AUDIT-C (Alcohol Use Disorders Identification Test), T-ACE (Tolerance, Annoyance, Cut down, Eye-opener), and TWEAK (Tolerance, Worry about drinking, Eye-opener, Amnesia, K/Cut down). Other screening tools used are 4Ps plus (Parents, Partner, Past, Pregnancy), TQDH (Ten Question Drinking History), CAGE (Cut down,

Annoyed, Guilty, Eye-opener), MAST (Michigan Alcohol Screening Test) and DAST (Drug Abuse Screening Test). The full AUDIT instrument, the abbreviated AUDIT-C, and single-question screening ("How many times in the past year have you had five [for men] or four [for women] or more drinks in a day?") have the best performance characteristics for detecting the full spectrum of alcohol misuse (Jonas et al. 2012). Screening, Brief Intervention, and Referral to Treatment (SBIRT) is an evidence-based practice used to identify, reduce, and prevent substance use disorders in different health-care settings. SBIRT gives health-care providers skills to discuss health behavior changes with their patients and has proven particularly effective at motivating individuals to change harmful substance use. SBIRT has three components: (1) screening to determine the severity of substance use; (2) brief intervention to build motivation through supportive conversation, and (3) referral to treatment directly linking the patient with needed services (SAHMSA 2009).

Documentation of the interview and confirmation or not of maternal substance use should be recorded and information regarding maternal substance use transferred to appropriate health-care providers (i.e., obstetrician, anesthesiologist, pediatrician) to ensure a continuum of care (Sarkar 2009).

Biologic Specimens

The use of biologic specimens to screen for substance use has inherent difficulties. It does not give information about use patterns, is variably accurate depending on substances screened for and testing used, and can cause unintended legal consequences. Maternal and neonatal urine screening are most commonly used and have the lowest cost but only provide information about use in the last part of gestation (exceptions to this are marijuana, the metabolites of which can be excreted for as long as 10 days in the urine of regular users and 15 or up to 30 days in chronic, heavy users, and benzodiazepines, which can be present in urine up to 30 days) and have low sensitivity (high false-negative rates). Meconium analysis is more sensitive and supplies information about use in the second and third trimesters when meconium is formed, but does not reflect periods of drug abstinence closer to delivery. Meconium may be difficult to collect (before contamination by transitional stool) and its passage may be delayed, particularly in preterms, delaying the diagnosis. Meconium testing has high false-positive rates; for example, for opiates, only 59 % of positives are confirmed by GC/MS (Brahm et al. 2010). Prior to testing, clinicians must be aware of legal requirements and the need for consent, which vary by state in the United States. Hospital policies should comply with local laws and avoid discriminatory practices.

138.2.4.3 Identification of the Individual Exposed Prenatally to Substances

In order to provide prevention and intervention programs to reduce the incidence of problems related to maternal substance use, it must be identified as early as possible. Obtaining an accurate history of prenatal exposure to alcohol and/or

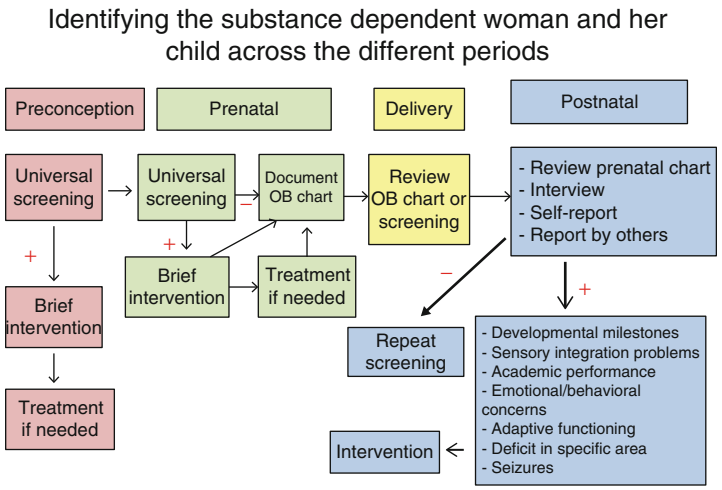

Fig. 138.2 Identification of the childbearing woman who uses/abuses substances should occur at several points during preconception and gestation and be multipronged, to include universal screening, review of the medical and social history, and maternal interview screening, as well as evaluation of the infant/child

other drugs is regarded as crucial for arriving at a diagnosis (Douzgou et al. 2012). Risk factors suggesting substance abuse during pregnancy include lack of prenatal care or late prenatal care, poor compliance with obstetric appointments, poor weight gain, cigarette smoking, skin infections, marks of injection (tracks), and preterm labor.

To date, there are no biologic markers to confirm or refute with certainty a syndrome or phenotype of children with problems related to prenatal drug exposure. This is a diagnosis of exclusion based on medical and alcohol/drug exposure history together with suggestive clinical signs. Infants with a suspected diagnosis of substance exposure or NAS should be evaluated using a scoring system such as the Finnegan. For children beyond the neonatal period, there are several nonspecific situations that can indicate suspicion of prenatal substance exposure in the absence of known causes, which include developmental delays, sensory integration problems, emotional and behavioral problems, poor academic performance, seizures, or deficits in specific functioning of the child (Fig. 138.2). The diagnosis of problems related to prenatal substance exposure is complex. Because it carries lifelong consequences, early recognition and treatment can result in a better outcome for the child that receives a diagnosis.

Underdiagnoses or overdiagnoses are not beneficial for the child or the family. The most important role of the clinician in the assessment of children with suspected problems related to prenatal substance exposure is to rule out alternative or coexisting diagnoses. Metabolic testing of urine or blood for other conditions and

imaging and/or chromosomal or SNP studies are a decisive approach in eliminating other causative factors including genetic abnormalities.

A history of prenatal alcohol exposure, necessary for a diagnosis of pFAS, ARND, or ARBD may be difficult or impossible to obtain. As a result, several scoring systems have been proposed, of which the 4-Digit Code (Astley 2006) and the Revised Institute of Medicine criteria (Hoyme et al. 2005) are the most widely used. The differential diagnosis includes only a small number of other dysmorphic syndromes, which can be excluded by a clinical geneticist. The American Academy of Pediatrics in concert with the Centers for Disease Control and Prevention created a schema to guide medical home providers through effective FAS/FASD screening, early identification, management, and referral (AAP and CDC 2006).

138.2.5 Interventions for PWSUD and Their Children

138.2.5.1 Preconception and Prenatal Counseling

Perinatal care providers have several opportunities during the preconception period and pregnancy to identify and assist women who have substance use problems. Those women found to have a positive screening for substance use can receive a brief intervention or be referred to receive a comprehensive diagnostic evaluation and intervention. This process can be facilitated by using the principles of motivational interviewing. Brief interventions that address substance use in a nonspecific way, in the context of several other potential health risks, may be useful. Brief interventions include short counseling sessions, feedback, advice, and goal-setting conducted by health-care providers. Even brief counseling has demonstrated effective in reducing the amount of drinking in pregnant women and the rate of morbidity in their offspring.

Pregnant women who are identified as having a substance use disorder should receive a multistep management approach that includes comprehensive individual and or group therapy concerning the adverse maternal and fetal/newborn impact of continued use and comprehensive prenatal care with identification of and intervention for medical and obstetric problems associated to substance use. Referral to a multidisciplinary team for drug rehabilitation and a high-risk pregnancy specialist for ongoing fetal surveillance should occur; appropriate additional referrals may include counseling to deal with preexisting trauma and or psychiatric comorbidity and assistance with other social determinants of health (e.g., food and housing) (Fig. 138.3), as women with fewer social supports are less likely to seek or remain in treatment. Additionally, partner participation in prenatal care and addiction treatment is very important to the woman's recovery; partner's active drug use has been associated with delayed treatment time for pregnant women seeking care. Comprehensive care, including health care and developmental and behavioral assessment, for existing children who may have suffered through the darkest days of their parent's addiction prior to their entry into medical care should additionally be incorporated into the care plan for any parenting woman.

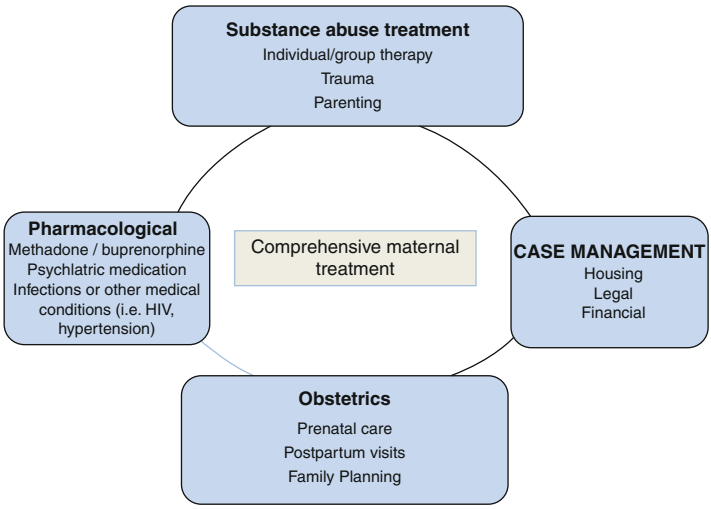

Fig. 138.3 Comprehensive treatment of the substance-dependent pregnant woman. Treatment of the pregnant woman who uses/abuses substances should be comprehensive in nature and incorporate behavioral treatment; medical/obstetric/psychiatric care with pharmacologic treatment, including methadone or buprenorphine maintenance, as warranted; and the identification and provision of social support structures

138.2.5.2 Pharmacologic Treatment During Pregnancy

Any pharmacologic treatment during pregnancy requires a clear and thorough discussion of the risk–benefits of the medication between the health-care provider, the mother, and the significant other when appropriate. Pharmacologic treatment for PWSUD includes medications for medical problems (i.e., HIV, hypertension), psychiatric comorbidities, and maintenance medications for the treatment of drug dependencies, such as in opioid-assisted therapy (Jones 2013). Daily maintenance with methadone or buprenorphine reduces the risk of relapse, increases retention in obstetric and substance abuse treatment, and may improve lifestyle for women addicted to opioids by reducing criminal activity and avoiding risks to the patient of association with a drug culture. Both medications must be viewed as a central aspect to treatment but should be given as part of a comprehensive treatment approach that also includes obstetrical care, medical care, case management, life and parenting skills, and counseling. These other components of care are needed to help empower women with opioid-use disorders to overcome the many complex, intertwining factors that served to set the context for their initial and/or continuing use of opioids. Although the benefits of treatment with methadone and buprenorphine are well known, a large number of infants exposed to these medications develop NAS. A study comparing the effects of these two drugs suggests that infants exposed to buprenorphine need less morphine for treatment of NAS and shorter duration of treatment and have shorter periods of hospitalization than children of mothers treated with methadone (Jones et al. 2010). The rationale for opioid-assisted therapy during pregnancy is to

prevent complications of illicit opioid use/licit opioid misuse and cycles of narcotic overdose and withdrawal in the mother.

138.2.5.3 Postpartum Care of the PWSUD

Comprehensive postpartum follow-up for PWSUD is necessary, with appropriate referrals to a primary care provider, a psychiatrist if needed, and social services when warranted to ensure that the newborn has a safe home environment. Working to ensure that women with substance abuse disorders engage in safe sex practices and family planning is a constant challenge; these women are disproportionately overrepresented among women with unplanned pregnancies and sexual violence.

138.2.5.4 The Mother/Child Dyad: Postnatal Period

Both maternal substance use and many of the medications used to manage the addiction and/or psychiatric symptoms have been associated with negative effects on the neonate (i.e., low birth weight, prematurity), NAS, and/or difficult adaptation of the newborn. Challenging neonatal behaviors such as irritability, uncoordinated movements, dysregulated sleep–wake patterns, hypertonicity, and autonomic signs of stress, frequently displayed by a neonate affected by prenatal substance exposure, can initiate altered caregiver behaviors, which have been considered an additional teratogenic effect of prenatal substance exposure. Children exposed to substances frequently have dysregulated nervous system functioning. They may have spontaneous or provoked changes in body tone, disorganized movements, and/or tremors that create great anxiety in the caregivers. They can have alterations in autonomic functioning and exhibit skin color changes (mottling, perioral cyanosis), tachypnea, fevers, or yawning/hiccuping. They can have difficulty managing a smooth transition between wake and sleep states and move rapidly from one extreme to the other without managing to achieve a quiet alert state, which is the state that infants use to provide cues to their caretakers. They can become overwhelmed by seemingly minimal sensory input, such as sights, sounds, touch, and/or movement, or display hyposensitivity to stimulation. They struggle with processing sensory information and either cannot process certain sensory inputs or they may react in adverse ways to even minimal sensory information. Learning to tolerate the early sensory experiences (i.e., touch, sound) is one aspect of developing early self-regulation. Problems with sensory integration are found in children that later present with learning disabilities and mood and behavioral problems. Infants with these difficulties require early recognition and appropriate interventions in order to facilitate a developmental trajectory toward more regulated, adaptive, and integrated responses that facilitate basic functions such as feeding, organized sleep–wake patterns, growth, and healthy child/caregiver interactions. Perinatal health providers should be trained in the special needs of these children to be able to help the infant and educate the parents.

All substance-exposed infants should receive non-pharmacologic supportive management of any symptoms beginning at birth regardless of the need for

medication for NAS. These interventions are designed to (1) individualize the care of the infant, based on behavioral observations, with the goal of promoting organization, physiological stability, and competence; (2) modify the environment to support autonomic, sensory, motor, and attention/interactive development; and (3) encourage parental involvement with their infant (Velez and Jansson 2008).

A child suspected of having NAS should be hospitalized for a minimum of 72 h for evaluation and identification of symptoms that may need pharmacologic treatment. This evaluation can be done using the Finnegan scoring system (Finnegan 1975) or a variant of it (Jansson et al. 2009). These tools are applied every 3–4 h for the infant's entire hospitalization. When the infant reaches a threshold score that indicates difficulties in feeding, sleeping, or interacting with their environment, medication is used. Medications most frequently used to treat the opioid-exposed infant are morphine sulfate and methadone (AAP 2012). Breastfeeding is not contraindicated in many substance-dependent women who are able to access treatment, which may include methadone or buprenorphine maintenance, and achieve sobriety and have no other medical contraindications to lactation, but each dyad should be individually assessed regarding their suitability for this practice (Jansson 2009).

The primary care pediatrician has an important role in addressing prenatal substance exposure, which includes ongoing assessment of the infant, his caregivers, and his environment (Jansson and Velez 2012). This includes (1) assistance with maternal difficulties surrounding her substance use/abuse (i.e., referrals to appropriate social services that can provide assistance with substance abuse treatment, psychiatric care, and contraceptive services) and awareness of how those difficulties impact the health and development of the child, (2) identification of infant/child difficulties related to exposures or parenting difficulties, (3) evaluation of his/her ongoing protection from situations related to drug dependence in his/her parents (i.e., violence exposure, safety issues surrounding maternal or paternal relapse to drug use, parental psychiatric issues), and (4) careful medical and developmental follow-up of the exposed infant (Behnke et al. 2013). Mothers of substance-exposed children may be afraid to seek evaluations and interventions (i.e., assessment for problems related to FASD) for fear of being labeled a "bad" or incompetent parent or due to her own difficulties dealing with the guilt for causing the problems in the child. Judgmental or punitive health-care provider attitudes will cause further reluctance on the mother's part to engage in necessary health care. Neurodevelopmental, behavioral, academic, and emotional problems in childhood related to prenatal substance exposure can have both lifelong and intergenerational effects. Identifying and addressing these concerns early in life is essential, not only for the individual child and his/her parent(s) but to break the multigenerational cycle of addiction and victimization that often exists in substance-using families. In these cases, pediatricians must be able to step out of their traditional role as health-care provider to the child only to recognize and address the issues that are of critical importance to pediatric health, namely, issues that involve principally the parent and the environment created by parental difficulties with addictions.

Substance-exposed children and their mothers may have CNS disabilities (either preexisting or due to drug use) that can range from subtle to serious, with affected individuals presenting variable combinations of emotional regulatory deficits, deficits in memory, information processing, social skills (including pragmatic language and social communication skills), attention, and executive functioning, as well as significant behavioral and mental health issues. As a result, the interventions for a child, adolescent, or adult affected by prenatal exposure and his/her family vary according to these factors. Interventions designed to address neurodevelopmental problems associated with substance exposure require multidisciplinary assessment and care that is individualized and unique to the dyad, coordinated, compassionate, and comprehensive.

138.2.5.5 Parenting in the Substance-Dependent Mother

Mothers of children prenatally exposed to drugs or alcohol may themselves have neuropsychological impairments that can affect their abilities to parent their children properly. These impairments can be caused by chronic substance abuse, psychiatric comorbidity, poor parental models and childhood adversities, and/or their own prenatal substance exposure (Rutherford et al. 2011). Substance-dependent women often have compromised judgment and difficulties with communication and conflict resolution and struggle to navigate their own personal relationships and safety issues while attending to their children's safety, attachment issues, and emotional dysregulation, all of which increase their vulnerability to maladaptive parenting (Hume et al. 2006) and continued drug use or relapse to drug use. Other frequent conditions such as lack of social support, abusive domestic relationships, involvement with the criminal legal system, homelessness, and poverty are major factors that, if not addressed, may contribute to dysfunctional parenting, child neglect, and maltreatment and to the cycle of intergenerational substance abuse, violence, and mental health problems. At a program level, parenting education for substance-dependent adults is essential in the treatment of themselves and their children. However, while the provision of information and support is necessary, it is not enough (Shonkoff 2012). The promotion of resilience in a substance-exposed child faced with the biologic vulnerability created by prenatal exposures depends upon the availability of parenting adults who can help children develop effective coping skills necessary to restore physiological and behavioral homeostasis and reduce disruptions in their developing brain circuitries. Essential to this process is the capacity of the parent to provide buffering protection for the children's developmental progress through their own skills which include parental self-awareness, self-control, problem solving, planning, monitoring, and self-regulation (Shonkoff 2011). These skills areas are frequently underdeveloped or altered in one or both parents. The likelihood is, therefore, relatively low that these skills will be sufficiently strengthened by the simple education about child development or parenting recommendations. Training or coaching strategies that center on the parental skill set that includes executive functioning, emotion regulation, and social skills offer a promising new direction that is worthy of investigation, especially for

parents whose needs are not sufficiently addressed by existing support. An example of this mother/child model may be found in the "Mothering from the Inside Out" program. In this model, substance-using mothers struggling to manage their addiction as they also parent their children participate in therapy focusing on problem solving and coping emotionally with the everyday stresses of being a mother. This program is based on an attachment-based intervention that focuses on building in the mother reflective functioning and the capacity to attend to her own and her child's mental states in order to promote secure attachment and emotional development in the dyad. These services are offered in conjunction with outpatient substance abuse treatment for the mother. Mother/child interaction is facilitated by a developmentally trained child care team, and the treatment center functions as a milieu that facilitates the dyad's regulatory functions (Suchman et al. 2011; Mayes et al. 2012).

In summary, the prevalence of use/abuse of psychoactive substances among women before, during, and after pregnancy remains high and constitutes one of the most common preventable causes of child morbidity. Studies looking at the costs of children affected by prenatal substance exposure show that the burden of care seems disproportionately high compared to the resources spent on education, prevention, and specific treatment. Prenatal substance exposure can disrupt fetal neurotransmitter systems, brain circuitry, and other important regulatory systems in ways that continue to influence physiology, behavior, and health at birth or decades later. Any health-care professional in contact with a childbearing-age or parenting woman and/or her child plays a critical role in screening women for substance use during pregnancy and initiating appropriate interventions, as well as in the early diagnosis and ongoing treatment of children affected by prenatal substance exposure both biologically and environmentally. Although identification and intervention for women and children affected by prenatal substance use is critical, primary prevention (reducing the number of women of childbearing age who abuse legal and illegal drugs) and secondary prevention (recognizing and reducing the use of drugs among pregnant women) are also necessary. Inclusion of repetitive counseling to abstain from alcohol and drug intake for women in the perinatal (preconception, pregnancy, parenting mother) health examination is essential. Men and women of childbearing age and the general population must be informed that no safe level of alcohol or drug consumption during pregnancy has been established. Services that enhance the mental health, executive function skills, and self-regulation capacities of vulnerable mothers, beginning as early as pregnancy, suggest promising strategies to protect the developing brains of their children. It is of extreme importance to raise awareness of the impact of alcohol/drug use and to encourage the use of effective screening tools to reduce the incidence of problems related to prenatal substance exposure, which can profoundly impact not only the individual and his family but the health care, education, and legal systems as well as society. Only through the cooperative investment of providers of all specialties can truly universal screening and intervention take place for these high-cost, high-risk families.

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Integrating Translational Science with Adolescent Addiction Treatment: Treatment Implementability and Relapse Prevention

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Contents

Abstract

The integration of translational science into adolescent addiction has the potential to greatly improve treatment outcomes and relapse prevention. This chapter highlights several promising substance abuse interventions for adolescents and ways to improve treatment outcome, implementability, and relapse prevention through integrating translational research findings into treatment. Areas of research that focus on potential behavioral and neurobehavioral targets have direct implications for treatment efficacy and build on the current treatments that have been successful. With a better understanding of these processes and their influence on treatment of youth, such findings may provide information on increasing treatment acceptability. This is of great public health importance, given the clear relationship between initiating, remaining in treatment,

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long-term abstinence, and relapse. Developmentally appropriate, targeted treatments are likely to be more efficient and potent, require less staff time, lead to less relapse, and, ultimately, reduce the burden on providers.

139.1 Introduction

The integration of translational science into adolescent addiction treatment is intuitively appealing. Comprehending this integrative relationship is important in terms of understanding adolescent substance abuse behaviors, treatment processes (e.g., outcomes, dropout, treatment implementability), and relapse. Further developing the integrative relationship by moving beyond descriptive studies to theoretically driven models of behavior change and treatment in adolescents has the potential to greatly improve treatment implementability and relapse prevention. However, to truly understand this relationship of integrating translational science with adolescent addiction treatment, it is important to first highlight current adolescent addiction treatments and explore potential theoretical frameworks that may guide this work. The purpose of this chapter is to highlight empirically supported addiction treatments for drug-abusing youth. In lieu of providing a theoretical explanation after every highlighted treatment, an executive summary of potential behavioral targets that show considerable promise in their integration will be provided at the end of the chapter. Finally, implications for treatment efficacy, implementability, and relapse prevention will be discussed.

The majority of treatments shown to work for adolescent drug abusers have been family-based therapies, although a few combined (e.g., MET/CBT) treatment packages have shown promise. A number of these therapies are highlighted below. For a comprehensive review of adolescent drug abuse treatments, please see Macgowan and Engle (2010), Rowe (2013), Waldron and Turner (2008), and Winters et al. (2011).

139.2 Treatment for Adolescent Drug Abusers

139.2.1 Family-Based Therapies

Family-based therapies primarily treat drug abuse indirectly, through improving family functioning, but also directly, through impacting each system in which the adolescent functions (e.g., family, school, extracurricular activities).

139.2.1.1 Multisystemic Therapy (MST)

MST is an individualized, intensive home-based treatment program that focuses on family, school, neighborhood, and the social network factors that contribute to antisocial behavior. The ultimate goal of MST is to improve family functioning and leverage these improvements to facilitate healthy and sustainable changes

in the youth's environment (Henggeler 2011). MST has a strong evidence base demonstrating treatment efficacy for substance-abusing and substance-dependent youth (Henggeler et al. 1999, 2002, 2006). Not only does MST decrease drug use, it also decreases days in out-of-home placement (Henggeler et al. 1999), violent crimes, and criminal arrests (Henggeler et al. 1999). In addition, research has shown that MST, in conjunction with drug court, may enhance substance use outcomes for alcohol and marijuana and that treatment fidelity may be linked with decreases in drug use and other outcomes (Henggeler et al. 2006). For reviews of this research, please see Sheidow and Henggeler (2008) and Henggeler (2011).

139.2.1.2 Multidimensional Family Therapy (MDFT)

MDFT is a comprehensive and multisystemic family-based, outpatient program. MDFT targets four domains: (1) youth as an individual and with family and peer group, (2) parent as an individual and within the family context, (3) family functioning, and (4) interactions between family members and key social systems (Liddle 2002). Studies have shown the efficacy of MDFT in reducing substance abuse (Liddle et al. 2001, 2008, 2009; Liddle 2002, 2010; Liddle and Dakof 2008), improving school performance (Liddle et al. 2001, 2009), and improving family functioning (Liddle et al. 2001, 2009) in polydrug users, as well as marijuana- and alcohol-only users. The reductions in substance use have been maintained up to 1 year following treatment (Liddle and Dakof 2002; Liddle et al. 2008) for high-risk early initiators (Liddle et al. 2009) and for youth involved in the juvenile justice system (Liddle et al. 2001). Furthermore, findings suggest that MDFT may be particularly useful in treating cases of high severity and frequency of use and comorbidity (Liddle et al. 2008). For an overview and review of findings from research on MDFT, please see Liddle (2010).

139.2.1.3 Brief Strategic Family Therapy (BSFT)

BSFT targets self-sustaining changes in the family environment. The main therapeutic techniques fall into three categories: (1) the therapist initially "joins" the family by encouraging family members to behave as they normally would while the therapist is present, (2) then he/she diagnoses repetitive patterns of family interactions, (3) and finally he/she restructures family dynamics to promote new, more adaptive patterns of interaction. The primary goals of BSFT are to eliminate or reduce the adolescent's use of drugs and associated problem behaviors ("**symptom** focus") and to change the family interactions that are associated with the adolescent's drug abuse ("**system** focus"; Szapocznik and Hervis 2003). In addition to efficacy for drug abuse treatment for youth (Robbins et al. 2011; Santisteban et al. 2003), BSFT is associated with high levels of engagement of family members (Robbins et al. 2011) and in improving conduct problems and delinquency (Santisteban et al. 2003) and family functioning (Robbins et al. 2011; Santisteban et al. 2003). BSFT has primarily been studied with Hispanic youth samples.

139.2.2 Motivational Enhancement Therapy (MET) and Cognitive Behavioral Therapy (CBT)

MET/CBT is a combined treatment package (Dennis et al. 2002; Sample and Kadden 2001). The initial sessions include MET, which aims to elicit intrinsic motivation to change substance abuse by resolving client ambivalence. CBT follows, with a focus on helping individuals become abstinent. The underlying assumption of CBT is that learning processes play an important role in the development and continuation of abuse and dependence and that these same learning processes can be used to help individuals reduce their drug use. Much of the evidence for the efficacy of MET/CBT for adolescence comes from the Cannabis Youth Treatment studies (CYT; Dennis et al. 2004). CYT consist of two large-scale studies of adolescent treatments. Two combinations of MET/CBT (MET/CBT5 – two individual MET sessions, three group CBT sessions; MET/CBT12 – two individual MET sessions, ten group CBT sessions) were found to be efficacious in treating adolescent marijuana abuse. Results favored MET/CBT5.

139.2.2.1 Improving Adolescent Treatments Through Translational Science

One approach to improve empirically supported treatments that exist currently is through the integration of translational science. Specifically, translational research is one way to guide the integration of neuroscience into the development, refinement, adaptation, and implementation of adolescent drug treatment. In other words, translation frameworks aimed at applying basic science to the development of treatments for disorders in clinical populations have considerable promise to enhance drug treatment efficacy, potency, implementability, and relapse prevention. For example, neurobiological research on brain plasticity has demonstrated that the brain circuitry changes as a result of *actual* behavior change that occurs during treatment (e.g., Kolb and Gibb 2003). Recent technological advances in structural and functional neuroimaging have made it possible to observe these brain circuitry changes and measure the associated behavioral changes that occur during the course of treatment, all of which have the potential to inform the treatment process.

Recent compelling data suggest that behavioral, neurobehavioral, and/or neuroendocrine targets (e.g., impulsivity, risk-taking propensity, delay discounting, sensation, and novelty seeking) play an important role in substance abuse/dependence, treatment dropout, relapse, and treatment outcome. There is great potential in research to understand the malleability of these neurobehavioral processes and in developing and testing novel treatments and/or modules that specifically target them. We will provide a brief summary of these potential processes below.

Impulsivity

One possible target that has been well studied and linked to addiction in youth is impulsivity. The focus on this behavioral index is not surprising, given that substance abuse and other comorbid conditions include impulsivity within the

diagnostic criteria. Further, substance use itself has been conceptualized as impulsive behavior (e.g., Lane et al. 2003; Reynolds et al. 2006). However, beyond the general documentation of impulsivity in drug-using youth (i.e., greater levels of impulsivity are related to greater levels of addiction; Kirby et al. 1999; Krueger et al. 2002; Moeller et al. 2001), there is reason to believe that levels of impulsivity may be differentially associated with variations in risk (e.g., injection drug users may have highest levels of pathology and impulsivity) and should be considered during treatment and in relapse prevention.

Understanding how addiction and impulsivity converge, as well as the contextual profiles in which they occur, would permit interventions to be targeted toward specific needs and goals for given individuals or subpopulations. Not only would this provide a strong theoretical framework, but it also would help to better individualize assessment approaches and evaluation throughout the course of treatment. It is essential for these assessment and evaluation tools in the treatment context to capture variables related to decision making (i.e., personality and behavioral) that have been linked to drug use in youth.

Risk-Taking Propensity

With regard to the intersection of impulsivity and treatment outcome, risk-taking propensity may be one potential predictor underlying treatment dropout or adherence. Traditionally, risk-taking propensity is conceptualized as one's decision to engage in a particular behavior that balances the probability of unpredictable rewards and punishments (Byrnes et al. 1999; Leigh 1999). For example, while drug use produces reinforcing effects, there remain potential but generally unpredictable punishers that may include compulsive drug seeking, withdrawal, adverse health effects, and criminal penalties. With respect to risk-taking propensity as a behavioral target in treatment, available studies indicate that engagement in risk-taking behaviors often is established during adolescence and remains as major contributors to the health problems of adults (Aklin et al. 2005; Lejuez et al. 2002, 2005, 2007; Mitchell et al. 2008). There is a clear need to develop assessment tools that can effectively identify adolescents most vulnerable for engaging in risk-taking behaviors and developing dependence. Indeed, the ability to prospectively predict future engagement in risk-taking behaviors would have profound effects on the ability to develop tailored treatment approaches. These elements need to be studied empirically and translated into developmentally appropriate interventions for adolescents.

Delay Discounting

Delay discounting (DD) is described as a choice preference between a "smaller sooner" reward and a "larger later" reward, with increased DD referring to a more rapid loss of value over time. Specifically, the relative inability to wait for a larger reward (delayed gratification) is often considered to reflect personality traits of impulsivity and a failure of inhibitory control. Extant data suggest that DD decreases with age (Steinberg et al. 2009) and that the greatest changes occur during mid-adolescence.

Increased "delay discounting" (DD), i.e., choosing the "smaller sooner" reward, is particularly severe in populations characterized by drug use, dependence, and other disorders characterized by poor self-control (Bickel et al. 2012). Repeated testing of DD behavior suggests that individual differences remain relatively stable between different potential rewards (Odum 2011). With respect to drug abuse findings, a recent comprehensive meta-analysis (MacKillop et al. 2011) of dozens of case-control comparisons indicated that 75 % of studies found (on average) more severe DD in the substance-using group compared to matched controls.

Several longitudinal findings also have indicated that DD behavior at baseline is moderately prognostic of initial drug use in youth (Audrain-McGovern et al. 2009) as well as predictive of relapse following substance abuse treatment (MacKillop and Kahler 2009). Researchers have begun to study the extent to which DD behavior is malleable with intervention, where specific training that targets working memory has spillover benefits to reduce DD behavior (Bickel et al. 2011). Because brain systems implicated in DD develop at different rates, adolescents may be particularly vulnerable to making poor decisions around substance use. The plasticity of DD during adolescence may provide a unique window to intervene and reduce DD. Germane to adolescent addiction treatment, the dual systems theory predicts that problematic DD behavior might be remedied by bolstering the executive system in some subjects, but tamping down the approach/impulsivity in other subjects (to the extent that these are separable).

139.2.2.2 Theoretical Perspectives

Given the promise of behavioral and biological targets as components of adolescent addiction treatment, it is important to highlight some theoretical perspectives that may be useful to guide this work. Although there are a number of theoretical approaches in the literature, a comprehensive review of each perspective is beyond the scope of this chapter. Instead, we will provide a sampling of perspectives that have been studied extensively and have the potential to be integrated into adolescent addiction treatment and relapse prevention.

From a developmental perspective, adolescence is a unique period of peak vulnerability for engaging in substance abuse (Ernst et al. 2006; Spear 2000). Adolescents are more at risk for initiating substance use and progressing toward dependence than adults (Chambers et al. 2003). This vulnerability for drug addiction may rely on similar features of reward function as those characterizing externalizing disorders. Therefore, examining normative neurodevelopmental changes in reward function may prove helpful in understanding mechanisms that underlie addiction. Following this idea, neuroimaging studies are beginning to shed light on the neurobiological development of reward function during adolescence (Bjork et al. 2004; Ernst et al. 2005; van Leijenhorst et al. 2006). These studies may greatly inform current knowledge on the development of reward-related disorders such as substance abuse and assist in tailoring developmentally appropriate treatments to enhance treatment outcomes and prevent relapse.

Another widely cited framework is the social-cognitive model (Bandura 2001). The social-cognitive model explains how people acquire and maintain certain behavioral patterns, while also providing the basis for intervention strategies. Although this model was not developed with specific reference to any one drug, it has relevance to and compatibility with translational science. In addition to providing adolescence with the behavioral means and other treatment resources, there is a sizable gap between simply possessing self-regulative skills and being able to use them effectively under difficult circumstances, which requires one to exercise impulse and/or self-control.

In line with a neurobehavioral perspective, increased risk for drug addiction may reflect a vulnerable reward system in adolescents, particularly among youth with comorbidity (Chambers et al. 2003). The pattern of the developmental trajectory of addiction may provide valuable information about the contribution of reward function of addiction and developmentally appropriate treatment strategies for youth. Two basic types of reward-related mechanisms have been proposed to underlie drug addiction, and these models are based on opposite assumptions. One mechanism describes a hyperactive reward system that results in the search for more rewarding stimuli. The other posits a hypoactive system that requires more reward exposure to maintain homeostasis. The latter model, also called the allostatic model, has been proposed by Koob (2002). Such a framework would predict enhanced reward consumption without leading to faster progression across addictive stages (Koob 2002; Spear 2000). Irrespective of which reward patterns are operative, having a better understanding of the characteristics of reward-related behaviors and susceptibility to addiction for youth has the potential to inform targeted treatments that integrate neurobehavioral findings.

139.3 Conclusion

This chapter highlighted several promising substance abuse interventions for adolescents and ways to improve treatment outcome, implementability, and relapse prevention through integrating translational science findings into treatment. Areas of research that focus on potential targets have direct implications for treatment efficacy and build on the current treatments that have been successful. Considering the context of the larger literature on impulsivity, risk-taking propensity, delay discounting, and drug abuse treatment, novel targets as core features of treatment have the potential to improve retention, compliance, long-term treatment outcomes, and implementability and relapse prevention. For example, youth with increased levels of risk-taking propensity may be prime candidates for specialized treatment and other supportive measures, whereas standard protocols of treatment may well be adequate for youth with lower levels of risk-taking behavior. With a better understanding of these processes and their influence on treatment among youth, such findings may provide information on increasing treatment acceptability. Additionally, the integration of these processes is of great public health importance,

given the clear relationship between initiating, remaining in treatment, long-term abstinence, and relapse. Developmentally appropriate treatments targeting individual differences in these processes have the potential for enhanced treatment implementability. These targeted treatments are likely to be more efficient and potent, require less staff time, lead to less relapse, and, ultimately, reduce the burden on providers. The series of studies and the corresponding theoretical perspectives of each, as covered in the chapter, suggest potential value of targeting youth with high levels of impulsiveness to receive modified and/or specialized treatment modules. Perhaps an emphasis on effective decision-making skills, risk modulation, behavioral control, and treatment adherence may be especially important in addiction treatment for youth. However, these are empirical questions that should be subject to scientific inquiry.

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Section XII

Education and Training

Nady el-Guebaly and Cornelis A. J. de Jong

Education and Training: An Introduction

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Nady el-Guebaly and Cornelis A. J. de Jong

This section on Education and Training appropriately concludes the textbook. Following the exposé of the breadth and depth of the knowledge base in Addiction Medicine, the first part of the section presents several select examples of the valiant efforts conducted in several countries to educate and train the next generation of practitioners in the field. Some countries focus on primary care, others have a focus on specialties. The process is universally incremental.

The first chapter by Drs. De Jong and Luycks describes the 2-year Dutch Master in Addiction Medicine (MIAM) leading to, in 2012, Addiction Medicine being recognized as a medical specialty by the Royal Dutch Society of Medicine (▶ Chap. 141, "Addiction Medicine Training in the Netherlands"). The curriculum involves a theoretical course of 1 day a week and training in clinical practice 4 days a week in accredited facilities by approved clinical supervisors. The competencies required are outlined and are concretized in 29 Characteristic Professional Situations (CPSs) in Addiction Medicine. For all these CPSs, tools are developed for assessment and examination.

The second chapter by Drs. Crockford and el-Guebaly reviews the core training requirements developed over the last 10 years under the purview of Canada's two colleges, the College of Family Physicians and the Royal College of Physicians and Surgeons (▶ Chap. 142, "Medical Education in Addiction and Related Disorders: The Canadian Experience"). There is no formal subspecialty recognition at this point with

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the colleges struggling with some 45 similar requests for subspecialty status from other fields. The training requirements and objectives in family medicine and psychiatry are detailed.

The third chapter by Dr. Welle-Strand describes the steep course towards recognition of Addiction Medicine as a specialty in Norway based on a governmental Drug Reform Action Plan initiated in 2007 (▶ Chap. 143, "Development of a Full Medical Specialty in Addiction Medicine: The Norwegian Experience"). The plan was pursued with the eventual support of the National Medical Association, the Council for Specialists and Specialist Education, and the Ministry of Health. The training requirements and competencies are being both developed and implemented.

The fourth chapter in this first part is by Drs. Parawita Ayu, Schellekens, Iskandar, Pinxten, and De Jong (▶ Chap. 144, "The Development of a National Training Program on Addiction Medicine in Indonesia"). It outlines the laudable efforts in Indonesia to replace the traditional criminalization of addiction by a public health approach with a training course based on the Dutch model. The Bandung Addiction Working Group has undertaken to start a national training program, including distant learning. However, a proposed short course is still seeking governmental support. Furthermore, the occasional 1-h lecture at the undergraduate level at the Atma Jaya University has been replaced by a 5-week elective. The course will be scientific, evaluated on its effectiveness on changing attitudes of future medical doctors towards addicted patients in a positive direction.

The struggle for recognition has been supported by the development of educational resources available to an international audience, and the section's second part describes examples of such resources.

For the last decade, the International Society of Addiction Medicine (ISAM) has undertaken to develop a test of knowledge based on a pool of 225 multiple choice questions with a committee chaired by Dr. el-Guebaly. Repeated administration of the examination to 110 applicants from 13 countries so far has demonstrated the validity of this process, along with challenges to be overcome.

The second resource by Dr. Bryant describes a project aiming at identifying an optimal pathway to navigate the extensive available literature as a part of Evidence-Based Addiction Medicine. Designed from the experience of Hubert H. Humphrey Fellows training in the United States and taking advantage of Open Access literature repositories, optimal resources available to translate research into practice are recommended.

The development under the auspices of NIDA of a network of International Fellowships for research training has added a much needed new resource for the development of an international workforce of investigators. The range of opportunities is described by Dr. S. Gust, the Program Director.

Another new resource has been the development of the Treatnet program under the auspices of both UNODC and WHO. Dr. Saenz et al. describe the experience gleaned from the project's results along with emerging themes and lessons from its implementation, including combating the social stigma attached to the field.

Last, but not least, the practice of Addiction Medicine as a resource in pain management has been identified as one of the new frontiers of the field. Dr. Murnion describes the curriculum developed by the International Association for the Study of Pain (IASP).

From this section on Education and Training, a number of conclusions emerge. The initiatives described are uniformly recent ones and are at various stages of development. Until recently, there was little international awareness of each other's national efforts, and it is hoped that the section will promote more international collaboration and support and may even be a catalyst for long-distance learning.

We still lack a clear picture of undergraduate education at various medical schools as in many countries each designs its own. This is important because almost every medical doctor will be confronted with addicted patients. A well-designed curriculum will presumably help to destigmatize addicted patients but will also bring to the fore that Addiction Medicine can be an interesting field for future doctors.

Consensual strategies are emerging. More and more countries seem to be adopting a framework of competencies similar to the CanMEDS model as well as education being perceived as a lifelong process.

Concerning the training in different countries, we must conclude that there is no "one size model fitting all." The journey towards specialty recognition must adapt to local educational and licensing requirements that govern the national practice of medicine. Opportunities must be seized, often as the result of societal peaks in awareness or workforce crises. Different career paths or remuneration issues may affect the optimal recommendations needed.

Some countries have adopted a focus on primary care; others have a focus on specialties including psychiatry, internal medicine, and community health; and most are adopting a two-prong approach. Addiction affects every medical practice.

The process is universally incremental and currently in transition creating unique challenges in implementation but also opportunities for international group support.

Addiction Medicine Training in the Netherlands

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Cornelis A. J. de Jong and Lonneke Luycks

Contents

Abstract

Since 2007 there is a full-time, 2-year professional training in addiction medicine in the Netherlands. In 2012 addiction medicine is approved as a medical profile specialty by the Royal Dutch Society of Medicine. The aim of this chapter is to describe the present status of the Dutch Master in Addiction Medicine (MiAM). In this competency-based professional training, theoretical courses are integrated with learning in clinical practice under guidance of an experienced clinical teacher. The theoretical courses consist of evidence-based medicine, communication and basic psychotherapeutic skills, neurobiology of addiction, addiction medicine, addiction and psychiatry, clinical leadership, and public health. The seven main competencies are concretized in so-called

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Characteristic Professional Situations (CPS) which are integrated in the personal education plan (PEP) and are evaluated by different ways of examining. The ways in which the residents are assessed and examined are described as well as the way in which the quality of the MiAM is managed.

141.1 Introduction

Addiction medicine should be made interesting for young physicians (DeJong and van de Wetering 2009; Soyka and Gorelick 2009). Therefore, training and research facilities for physicians are to be improved to stimulate their interest in this challenging area of medicine. In this chapter we will describe the way of training physicians in addiction medicine in the Netherlands. The professional training to get a Master in Addiction Medicine (MiAM) started in 2007 and is competency based from the start (Carraccio et al. 2002). This means that the residents are trained to combine knowledge and skills in the context of their daily work in addiction treatment services or other mental health facilities. The theoretical courses are given 1 day per week; skills are trained in every practice by a clinical teacher with due experience in addiction medicine. The historical background is described in detail elsewhere (DeJong et al. 2011).

In 2005 the medical directors of the leading addiction treatment facilities took the initiative to develop a nationwide professional Addiction Medicine Training (AMT) course for promising physicians.

This initiative fitted well in the growing attention in medical associations and employers in mental health and addiction treatment field to improve the quality of care given by professionals.

Between 2006 and 2007 we developed a state-of-the-art curriculum for a 2-year full-time professional training in addiction medicine. SPON Post Academic Education in Health Care organizes the MiAM. SPON is a cooperation between the Radboud University and the Foundation of Organizations of Post Academic Education in Health Care in Eastern Holland (www.spon-opleidingen.nl).

During 2007–2012, a lot of accomplishments were made (DeJong et al. 2013a). The first group started in 2007, and since then, five groups of approximately 20 medical doctors each started with the MiAM. In 2012 we had a pool of 23 training facilities. Several graduates are now involved in the MiAM as lecturers or clinical teachers; some of them are Ph.D. candidates. Parallel to the course for the residents, an intensive training program for clinical teachers was developed and implemented. The MiAM is now embedded in the Faculty of Medical Sciences within the postgraduate curricula of the unit Primary Health Care together with the curricula for general practitioners, occupational medicine specialists, and geriatric medicine. To become approved by the Royal Dutch Society of Medicine (RDSM), an extensive educational program had to be written (Luijkx 2012). Based on this program, addiction medicine is recognized as a medical profile specialty in 2012, and the register is opened for qualified doctors in June 2013. This means that residents in the Dutch MiAM can be registered as soon as they are graduated and

that they have the same status as other profile specialists. The Dutch medical system is comparable with the ones in other EU members.

In this chapter we will describe the present state of affairs of the Dutch MiAM and the status of addiction medicine specialists in medicine.

141.2 Master in Addiction Medicine (MiAM)

141.2.1 Addiction Medicine Training: State of Affairs

141.2.1.1 Competencies of Addiction Medicine Specialists

The aim of the professional training is to teach the residents to become competent addiction medicine specialists in the addiction treatment and mental health facilities. To find out at the start in 2006 what should be integrated in our theoretical program, we made use of several sources in major textbooks (Levin et al. 2004; Chappel 2005).

In our opinion a competent medical doctor is able to perform a professional activity adequately in a specific context. He can do that because knowledge, insights, skills, personal attitude, and characteristics are present in an integrated way (Carraccio et al. 2002).

The competencies for the addiction medicine specialist are derived from the model of the Royal College of Physicians and Surgeons of Canada (Frank et al. 1996), the CanMEDS 2005 Physician Competency Framework "Better standards. Better physicians. Better care" (Frank 2005), the Profile of the Dutch addiction medicine specialist (VVGN 2008), the Dutch Profile Psychiatrist (NVVP 2005) and international programs for addiction psychiatry (http://www.acgme.org/acWebsite/home/home.asp), criteria for international certification in addiction medicine (http://www.isamweb.org), and the SAMHSA (Center for Substance Abuse Treatment 2006).

The goals of qualification in seven domains of competency are summarized in Table 141.1.

141.2.1.2 Educational Concepts

In the MiAM, we use a "student-centered approach" (Mickelson et al. 2009); this means that the resident takes an active and central role in the learning process. For example, the individual goals of every MiAM resident are (self)assessed at the start of the training and are written down in the personal education plan (PEP) together with the planned activities to reach these goals. They are based on the seven aforementioned competencies. The PEP is an instrument for the resident to design their learning process and for the clinical teacher to monitor this process.

Critical reflection plays an important part in the curriculum. The ideal process of reflection is described by Korthagen (1992). The model is based on Kolb's experiential learning cycle (Kolb 1984) (see Fig. 141.1) that involves concrete experience followed by observation and experience followed by forming abstract concepts followed by testing in new situations.

Table 141.1 Goals of qualification of addiction medicine specialists in seven domains of competency

Domain of competency	Goal of qualification
Medical practice	The addiction doctor shows professional conduct and has knowledge and skills to the position of the field. It allows him/her to collect data and to interpret them, so that diagnostic and therapeutic and evidence-based decisions can take place within the boundaries of the discipline and expertise. He/she gives up-to-date effective care, in an ethically responsible way. He/she combines his own clinical expertise with the most recent scientific findings and the preferences of the patient
Communication	To ensure that the levels of high quality of patient care and patient satisfaction are maintained, the addiction doctor communicates in an effective and respectful way with patients and their environment. The addiction physician practices a clear, transparent, effective, and efficient way of communication. It involves both verbal and nonverbal communication. He/she takes care of responsible shared decision-making procedures
Collaboration	The addiction doctor knows the structure of health care, social services, and the organization. He/she participates in a network of functional relationships and makes optimal use of available expertise of other professionals
Knowledge and science	The addiction doctor is characterized by his/her commitment to increase his/her knowledge and skill in addiction medicine. He/she may raise questions emerging from his/her clinical practice and is able to answer them following the principles of evidence-based medicine including critical appraisal of the scientific literature. The addiction doctor promotes both his/her own expertise in the field of addiction medicine and also that of all professional fellow actors. He/she will preferably engage in scientific research projects
Operating in the social domain	The addiction doctor is able to weigh the interests of the patient in relation to the interests of other people asking for help and other social interests. Central is practicing in such a way that it meets the requirements of the medical profession and the society in general. Included in the social and cultural context are knowledge of medical ethics, law, and legal aspects
Organization of care	To be able to function efficiently and effectively as addiction doctor, he/she endeavors to optimize the healthcare organization he/she is working for. The addiction doctor is able to manage his/her own work, as well as those of others. The addiction doctor takes decisions relating to the use or deployment of resources and staff, setting goals and priorities, and making policy, and he/she organizes the work to a balance between professional practice and the need for further development of themselves and the organization
Professionalism	The addiction physician provides patient care in an honest, sincere, and committed way. The aforementioned competencies are integrated in an adequate way. He/she takes responsibility for his/her actions and keeps the right balance between personal and professional roles. He/she knows the limits of his/her competence and acts within it or calls in other experts. He/she puts himself on testable. He/she records in a responsible manner patient data. He/she participates in the scientific society of addiction medicine. He/she recognizes ethical dilemmas, has insight into the ethical standards, and adheres to the law. He/she is aware of his role model within health care

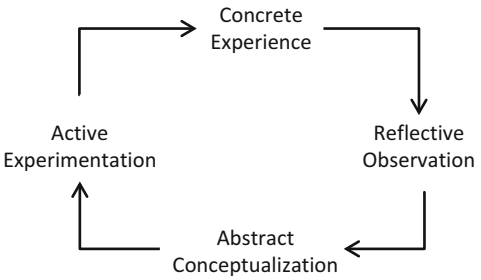

Fig. 141.1 Kolb's circle of learning

Kolb describes the force of experience and reflection on that experience: "Immediate concrete experience is the basis for observation and reflection. These observations are assimilated into a theory from which new implications for action can be reduced. These implications of hypotheses then serve as guides in acting to create new experiences." This experiential learning cycle shows close resemblance with Popper's evolutionary approach of objective knowledge (Popper 1973) and fits well with the basic of Evidence-based medicine (Sestini 2010).

The residents use three important sources of input in their learning process. They are stimulated to reflect on their own experiences in clinical practice; they can make use of the extensive experience of their clinical teachers and of the scientific knowledge of the teachers in the theoretical course. In the curriculum these three aspects are integrated. The whole training is a process of bringing practical experiences into the theoretical course and vice versa. It's a permanent, iterative process of education. The clinical teachers, employees of addiction treatment centers, and the theoretical teachers strengthen this iterative process with their knowledge about practice and theory. The level of knowledge and practical work is examined constantly, for instance, by means of evaluations of assignments, presentations, and video recordings.

141.2.1.3 General Aspects Program of the MiAM Program

The curriculum of the 2-year MiAM is divided into a theoretical course at the Radboud University in Nijmegen 1 day a week and training in clinical practice 4 days a week in addiction treatment facilities or in general mental hospitals with a specialized department for psychiatric patients with co-occurring substance-related disorders. Both aspects are highly integrated as is described in the Training Plan for Addiction Medicine, developed by the Dutch Society of Addiction Medicine (Luijkx 2012).

The MiAM training is designed along six central themes: diagnosis and intake, treatment, psychiatric comorbidity, somatic comorbidity, public health and prevention, management, and safety. These themes are integrated in the six modules of the theoretical course. For all themes the competencies are described in more or less general terms. For instance, in the theme diagnosis and intake, the competency communication is divided in ten phrases such as "He uses

motivational interviewing in the diagnostic phase and is able to handle the five core skills of motivational interviewing." It is quite hard to formulate more exactly what a resident has to learn. Therefore, 29 Characteristic Professional Situations (CPS) in addiction medicine are defined, ranging from "an alcoholic patient with impairment in executive functions" to "an addicted pregnant woman with ongoing harmful substance use for the fetus." For each CPS the knowledge aspects to be addressed in the theoretical courses are described as well as the competencies that are to be observed in clinical practice. For both aspects the ways of assessment and examination are described in detail in a test-book.

141.2.1.4 Starting a Learning Group

In the 2-year course in addiction medicine, the residents start the first and second year with a retreat of 3 days at a monastery. The first retreat focuses on getting to know the other trainees and the trainers. Therefore, the more serious parts, such as short academic lectures and role-playing, are alternated with group activities like singing, dancing, and performing. This is in part based on the philosophy that learning is fun. However, the goal of the exercises is also to raise the awareness of the verbal and nonverbal communication of the resident on a patient as partner in a conversation.

141.2.1.5 Theoretical Courses in AMT

The theoretical part of curriculum is organized in six modules (Table 141.2) with the following main topics:

1. Evidence-based medicine, communication, and interaction
2. Neurobiology of addiction
3. Addiction medicine
4. Addiction and psychiatry
5. Public health
6. Clinical leadership and management of care

The first five modules are introduced in the first year and are explored in depth in the second year. The sixth module is given in the second year. For all modules detailed course books are written by the teachers and are available in Moodle, our digital learning management system (LMS). Moodle is a free web application of such an LMS. It offers not only the possibility for placing course books in it but also for sending assignments to residents, for sending them back to the teachers, and for reviewing them by the teachers. All residents can make use of an iPad in the classrooms.

141.2.1.6 Training in Clinical Practice

All potential clinical training facilities are visited and inspected before they are certified as such. The inspection is carried out according to a checklist approved of by the professional group and that follows the guidelines of the Dutch Medical Society.

Table 141.2 Examples of the themes in the six modules of the MiAM

Module	First year	Second year
Evidence-based medicine (EBM)	How to practice EBM	Writing a single-case study based on EBM principles
Communication and interaction	Motivational interviewing	Individual coaching
		Family and system encounters
		Dealing with moral dilemmas
Neurobiology of addiction	Neuroembryology, neuroanatomy, neurophysiology, neurotransmission, neurogenetics of addiction Neuropharmacology of main psychoactive substances	Neurobiology of related psychopathology (i.e., aggression) and psychiatric syndromes (i.e., ADHD, PTSD, bipolar disorder, OCD)
Addiction medicine	Epidemiology, assessment and diagnosis, and approaches to management of the main psychoactive substances (detoxification, relapse management, maintenance treatment) according to guidelines	Assessment, diagnosis, and management of substance-related disorders and related somatic syndromes (internal medicine, neurology, gynecology) according to EBM principles
Addiction and psychiatry	Psychiatric assessment and diagnosis, integrated treatment for dual diagnosis, involuntary treatment, pharmacotherapy	Assessment, diagnosis, and management of substance-related disorders and related psychiatric syndromes (autism, schizophrenia, personality disorders, anxiety and mood disorders, ADHD, and PTSD)
Clinical leadership and management of care	Knowledge and skills for leadership, development of professional attitude, facilitation of collaboration, and strengthening the organization and for improving professional communication, development, and maintenance of a continuum of care shared with professionals, patient, family/environment, and organizations/institutions involved in prevention care and treatment of addiction	
Public health	Principles of general public health; international perspective; funding of healthcare system; juridical framework; general mental health care; epidemiology, prevention, organization, and finance of mental health care; Dutch policy of addiction and addiction care; disease management	

Evaluation of the professional, scientific, and educational qualities of the clinical trainer is an important part of the inspection. At the start of the MiAM training, there were no formally trained clinical teachers so a teaching program for the trainers accompanies the residents' professional training. Therefore, all clinical teachers are involved in a parallel training program to improve their qualities on these three domains.

Working with addicted patients is challenging for the young professional and stirs a lot of reactions in healthcare providers including medical doctors (Forrest 2002; Imhof 1995). Therefore, all residents have an individual psychotherapeutic

supervisor. During 60 h, spread over the 2 years, they can reflect on their own functioning in relation to patients, colleagues, managers, and so on. The supervisors are highly skilled psychiatrists with a psychotherapeutic background and not in a hierarchical position towards the resident.

The training in clinical practice is given by a medical doctor with extensive experience in addiction medicine or addiction psychiatry. The clinical teacher helps the resident to bridge the gap between theoretical knowledge and practical experiences. To do this in an optimal way, the clinical teacher has full access to the LMS of his or her resident. At the start of the professional training, the clinical teacher helps the resident to make up the PEP. This personal plan is evaluated and adapted at the end of the first year and is used as an instrument for testing the competencies at the end of the second year. In weekly meetings with the resident, the clinical teacher makes use of direct clinical exposure, video recording of encounters, examination of taped sessions, and a standardized instrument on nonverbal communication, interpersonal behavior, and motivational interviewing skills (Norcini 2003) to give corrective and normative feedback.

141.2.1.7 Integration of Theory and Practice: Evidence-Based Medicine and Conversational Skills

Besides the six central themes, the curriculum has two cornerstones: evidence-based addiction medicine and communication and psychotherapeutic skills.

The principles of evidence-based addiction medicine are cornerstones for the six modules of the theoretical course and for the practical training. Firstly, the theoretical course is given by experienced researchers who are preferably active in patient care. On the other hand, the clinical teachers are stimulated to become active as researchers and in scientific writing. Secondly, we use national and international evidence-based guidelines if available for well-defined diagnostic and therapeutic interventions. Thirdly, the residents are trained in evidence-based medicine as initially defined by Sackett et al. (1997; Scott Richardson et al. 2007). They learn how to develop searching strategies for finding answers on questions from their own consulting room and appraising in a critical way scientific publications found (CAT) and then applying these results into daily practice. Thus, evidence-based addiction medicine is a goal in the sense that they practice addiction medicine according to accepted guidelines, but even more important it is a method for reducing their insecurity in everyday practice by means of searching professional literature, critically appraising the findings, and applying it in their own practice. In all parts of the theoretical curriculum, the residents practice these EBM competencies in an assignment in which they have to perform a literature search and a CAT for one of their own clinical problems. Finally, the students have to write an EBM scientific paper in the format of a single-case study that will be peer reviewed and has to be accepted for publication. The papers of the first groups are published in a book (DeJong et al. 2009). The residents get support in scientific research and writing by experienced scientists.

Just like evidence-based medicine, conversational skills are of the utmost importance for effective and high-quality care for patients with substance-related disorders. Communicational and psychotherapeutic skills are basic skills for an addiction medicine specialist. Communication and motivational enhancement are essential parts of the daily work for they are integrated in the training of all residents in medicine (Leung et al. 2009). Details of this important part of the MiAM are described elsewhere (DeJong et al. 2013b).

Most residents in addiction medicine don't have an educational background in such skills. Therefore, we start the 2-year curriculum with an intensive 3-day retreat focusing on conversational skills. In a competency-based training, the first question should be how experienced the residents are at the start of the training? The assumption is that different residents, with different backgrounds, have different entrance levels. This becomes clear during the first training retreat. Three trainers give short introductory lectures on general aspects of medical consultations; motivational interviewing, interpersonal communication, unconscious feelings, and body language are followed by role-playing. During role-plays every resident plays the role of one of his or her own patients. Another resident plays the role of the doctor or therapist. At the end of the retreat, all residents receive oral and written comments on their skills and indications for improvement. The resident integrates these goals in their personal education plan (PEP).

After the introductory retreat, the residents make videotapes of their consultations in everyday clinical practice and discuss them with their clinical supervisor and their personal psychotherapeutic supervisor. After 1 year their skills are examined by their clinical supervisor in a formative way. The results of the examination play an important role in the decision if they are to be accepted for entering the second year of the MiAM.

In a second intensive 3-day retreat for the residents that have passed their examination at the start of the second year, their skills are explored intensively in role-playing sessions. Each of the three trainers focuses on one aspect of conversational skills: motivational interviewing, interpersonal interaction and unconscious feeling, and body language. Again the residents receive oral and written comments on their skills and indications for improvement, and they have to write an evaluation themselves. They are invited to discuss these comments and self-reflection with their clinical and psychotherapeutic supervisors. At the end of the 2-year course in addiction medicine, their skills are examined resulting in a "yes" or "no" for passing their final exam. The final assessment of the conversational skills is done by judging two video fragments of 10 min of conversation between the resident and a patient by four examiners. The assessment is done with a standardized instrument, the Quality Aspects of Professional Communication (QAPC) (DeJong et al. 2013b), consisting of five subscales: general aspects of conversation (GAC), nonverbal communication (NVC), motivational interviewing skills (MIS), clinical skills (CS), and interpersonal behavior skills (IBS). The inter-rater reliability of the QAPC is good for the total score (ICC = 0.79) and good to fairly good for the subsequent subscales (ICC_{GAC} = 0.81; ICC_{NVC} = 0.68; ICC_{CS} = 0.68; ICC_{CS} = 0.67 and ICC_{IBS} = 0.64).

141.2.2 Assessment, Examination, and Quality Management

Assessment is a powerful tool for the student to support its development. It gives information about their achievements or where gaps may occur. In competency-based learning, ongoing assessment is the base of the learning concept. Especially the clinical teacher has to find out together with the resident what the level of mastering competencies is. They can use the following levels of mastering to find out in what way the resident can start practicing in a safe way the CPS:

1. The resident has adequate knowledge of the subject of a CPS.
2. The resident can perform the professional activities associated with this theme under strict supervision.
3. The resident can perform professional activities under limited supervision.
4. The resident can perform professional activities without supervision.
5. The resident supervises and teaches others effectively in the professional activities associated with this theme.

In the MiAM both summative and formative assessments are used, each with a different purpose. Formative tests are aimed at development. It provides feedback regarding the learning process. The key question is what can the student perform/answer already and what not yet? The focus in summative tests is on determining what the student has learned at a given moment. It has a selective purpose. The key question is can the student perform/answer what is asked for yes or no?

Table 141.3 shows the formative and summative tests that are represented in the theoretical course and in clinical practice. Assessment, especially formative assessment, is part of the daily routine and of the observation of CPS. At the end of the first and the second year, a summative overall assessment is held in which all the study results of theoretical course and clinical practice are weighted. The portfolio based on the personal education plan is an important tool to do this. After the first year, the overall assessment provides information whether the student is allowed to start the second year and if so what his or her goals for the second year could be. After the second year, it has to give the input for the examination board whether the student can graduate or not.

The quality of the MiAM course is monitored and evaluated by means of several instruments.

For the six modules of the theoretical courses, standard evaluation forms are used. These forms are developed especially for all post-academic training programs of the educational training center SPON. The general questionnaire covers 22 questions (five-point Likert scale) on the teachers' quality, the content of the course, and the relevance for the clinical practice. Besides the fore written questions, the residents can give written comments. The results of each evaluation are discussed with the teachers and may lead to changes within the course.

An important factor of success of the training is the quality of the relationship between the resident and the clinical teacher. The clinical teacher is evaluated yearly by the resident in a structured way (Lombarts et al. 2007). The questionnaire

Table 141.3 Overview of the training program, assessment, and examination

Assessment and examination	First year					Second year				
Theoretical course In-between assignments	Module 1	Module 2	Module 3	Module 4	Module 5	Module 1	Module 2	Module 3	Module 4	Module 5
Theoretical course Final assignments	Module 1	Module 2	Module 3	Module 4	Module 5	Module 1	Module 2	Module 3	Module 4	Module 5
Progress interview with Clinical teacher (PEP*)	1 hour a week					1 hour a week				
- portfolio assessment - reflection - competencies - professional functioning - CPS** (10-12/year)										
Psychotherapeutic supervision sessions	30 hours a year					30 hours a year				
Psychotherapeutic supervision Amount of sessions, quality of learning process and development										
Formal scoring conversational skills QAPC*** ()	At least 6 a year				6	At least 6 a year				6
Master proof: video assessment conversational skills						1				2
Master proof: peer-reviewed scientific article										

Red: summative
Green: formative

*PEP=Personal Education Plan, **CPS=Characteristic Professional Situation, ***QAPS=Quality Aspects of Professional Communication

consists of 26 questions (five-point Likert scale) covering educational climate, personal treatment, communication about learning goals, assessment, feedback, role model and organization, and context. The data are used individually for the communication between the resident, clinical teacher, and principle lecturer. The first results of the first two groups (2007 and 2009) show that the residents are quite satisfied with the general quality of the clinical teachers as is expressed with a 4.2 on a scale ranging from 1 to 5.

The quality of the personal psychotherapeutic supervisor was explored by one of the residents, as a part of the scientific EBM paper he has to write for the MiAM (Reifenschweiler et al. 2012). It comes out that that in general the residents ($N = 19$) are quite satisfied with a mean score of 7.6 (0 = very poor – 10 = excellent). Despite the good quality 7 out of 19 residents indicate that they lack supervision issues. Some residents called their supervisor "short-sighted" and "self-gratifying". These bottlenecks are congruent with the literature (Van Staveren and VanOs 2009).

141.2.3 Relation with Other Professional Groups

The Dutch Society of Addiction Medicine (VVGN) and the Dutch Society for Psychiatry (NVVP) cordially support the MiAM. Specialists in addiction medicine could best be described as specialized generalists, meaning that they know a little (but enough) about many things. This is in contrast with specialized specialists who know almost anything about a very few things. Addiction medicine specialists

should be competent to recognize somatic and psychiatric co-occurring disorders besides the substance dependence syndromes as such.

The background of the residents is described elsewhere (DeJong et al. 2013a). In the first groups, medical doctors with already a career in addiction medicine entered the MiAM as well as medical doctors with a refugee status, and they are not allowed to continue working in their original specialty. In the last training groups, more young doctors entered the MiAM who recently graduated from medical school. In our opinion the last group is favorable for the further development of a new specialty.

After graduation and registration, the overlap in working field between addiction medicine specialists and psychiatrists is the most obvious. Since the start of the MiAM, a discussion is going on about who will be in charge in what domain. Happily we notice that in most facilities a constructive and respectful collaboration develops between the specialist in addiction medicine and the psychiatrist. There is less discussion about domains with general practitioners or medical specialists such as neurologists, internists, and gynecologists. In the addiction treatment facilities, medical doctors work together with clinical or general healthcare psychologists. The content of the work of each of these professional groups differ enough to recognize them as separate professionals. If there are problems between them, it has more to do with who will be in charge than with the level of competencies.

141.2.4 Funding

There is no governmental funding for the professional training yet, so the costs are brought up by the treatment centers. The direct costs to be paid at the educational center SPON amount to 8.500 euro per year per resident. The indirect costs consist of time the clinical teacher and the supervisor spend at the training of the resident and the time the resident follows the theoretical course (1 day a week) and is working on practical assignments. Usually this time is spent at the treatment of patients. Furthermore, the treatment centers must update their library and gain access to electronic libraries to fulfill the requirements of EBM. Finally, most of the treatment centers offer addiction medicine specialists a higher salary after graduation.

141.3 Conclusion

We developed in quite a short time a competence-based professional training program for addiction medicine in the Netherlands. In almost 6 years, four groups graduated; the fifth group will finish in December 2015. We can conclude that the MiAM is answering the needs of the mental health and addiction treatment field. The next step is to formulate the criteria for reregistration of all addiction medicine specialists in the profile register of the Dutch Society of Medicine. Furthermore, for the future of professional medical specialists in addiction medicine, it seems to us

important to get to know more about the international development of training programs in addiction medicine. The reason for sharing this information is that we want to be involved in a shared European or even a global initiative to train certified medical specialists in addiction medicine. The exchange of knowledge and experience in joined forces is absolutely necessary to accomplish such an endeavor.

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Abstract

Historically, the medical education in substance-related and addictive disorders in Canada has been disproportionately limited in residency training programs compared to other major illnesses and disorders. While currently in Canada, there is no formal subspecialty recognition or designation of addiction medicine or addiction psychiatry, over the last 10 years there has been increasing interest by the College of Family Physicians of Canada (CFPC) and formal establishment by the Royal College of Physicians and Surgeons of Canada (RCPSC) of core training requirements for addictions to be met during residency training in order to qualify for certification in family medicine and psychiatry, respectively. Proposed components for the curriculum for substance-related and addictive disorders applicable to family physicians and their challenges in their

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implementation are described. Established curriculum and training requirements for psychiatrists are then described with specific content areas, and means for Canadian residency training programs to meet these requirements are reviewed. Ultimately, it is hoped that as both family physicians and specialists build on the training requirements, their impact will broaden and lessen the gaps in care present for patients with addictions.

142.1 Introduction

Canada is the second largest country in the world by size but has a relatively small population of 34.5 million people. The country is divided into provinces and territories each having jurisdiction over how health care is delivered within the confines of the Canada Health Act. Provinces and territories are allowed to focus health care resources to identified priority areas based on regional need, but the Canada Health Act helps maintain a remarkable amount of general congruence in the delivery of health care. Core health services are publically funded with most patients receiving care by this means. More for the mind is the core report credited for the inclusion of mental health and addiction within the national health care scheme (Tyhurst et al. 1963). In Canada, parity of coverage exists for the treatment of addiction and psychiatric disorders equivalent to other medical diseases, but many addiction treatment services also exist outside of the publically funded health care system, where patients or families pay via private insurance, contracts, or directly out of pocket.

In Canada, substance related and addictive disorders are estimated to affect one out of every seven persons in their lifetime (Veldhuizen et al. 2007), where the annual societal cost is estimated to be 40 billion dollars annually (approximately $1,000 per person in Canada) (Rehm et al. 2007). Not unique to Canada, most persons with addiction do not receive any treatment at all or, if they do, often report unmet needs (Harris and Edlund 2005; Urbanoski et al. 2007; CASA 2012. Most of the approximately 75,000 physicians in Canada (physician to population ratio: 1 per 467) encounter patients at risk for or have active addiction (Canadian Institute for Health Information 2009). While up to 20 % of all visits to a family physician's office are either directly or indirectly related to addiction (Bradley 1994), the skill set of this large physician group to appropriately screen, identify, motivate, treat, and/or refer is limited (Midmer et al. 2002). A next level of addiction medicine practitioners involves some 1,150 mostly part-time family physicians who focus on the management of opioid dependence at methadone clinics (national mean = 47 patients per physician, SD +/−41.5) (Luce et al. 2011). Knowledge and skills in addiction beyond methadone prescribing are variable given that the completion of a 1-day course is only required to acquire a methadone exemption from the provincial/territorial college level for patients with opioid dependence. A much smaller group of family physicians focus full-time in the field and address a broader range of addiction issues. Among the specialties, psychiatry provides the majority of the specialist services in addiction, with more limited services provided by internal medicine, reproductive medicine, and pediatrics. The group of full-time

family physicians and specialists focusing on addiction medicine may account, in all, for only some 200 physicians where estimates are based on membership in national associations. Thus, despite parity in coverage for persons suffering from addiction, access to physician-led medical care may be limited by the relatively small number of physicians practicing in addiction medicine, potentially further contributing to the limited numbers of patients entering evidence-based treatments.

Reflecting and potentially directly contributing to unmet treatment needs, training in the management of addictions for family physicians and in the medical specialties has been disproportionately limited in residency training programs compared to other major illnesses and disorders (Gunderson et al. 2008). Until recently, few residents received training in addictions unless elective experiences were pursued. Moreover, a lack of experienced faculty, negative attitudes towards addicted patients, lack of adequate curriculum, and poorly defined educational goals and requirements have been identified as factors leading to the lack of training in addictions (Gunderson et al. 2008).

Two separate national colleges set and oversee the standards for the training of physicians in Canada. Family physicians (otherwise known as general practitioners or primary care providers) require 2 years of postgraduate training followed by a certification exam before practice eligibility and are overseen by the College of Family Physicians of Canada (CFPC). All medical and surgical specialties require at least 5 years of postgraduate training, then must pass a certification examination before practice eligibility. Medical and surgical specialists are overseen by the Royal College of Physicians and Surgeons of Canada (RCPSC). Due to the country's vast geography, remote areas, and concern that too much specialization may potentially lead to a loss of continuity in care and increased "fragmentation," both colleges have promoted the training of "generalists" and "sophisticated generalists," respectively, rather than promote further subspecialization. Despite this, both colleges have, over the last 10 years, been challenged by the request for recognition by an increasing number of specialty practices, including addiction medicine. As there is no formal subspecialty recognition or designation of addiction medicine or addiction psychiatry in Canada at present or requirement for these to focus practice in addictions, physicians pursue recognition then via sitting certification examinations with the American or International Societies of Addiction Medicine, where the Canadian Society of Addiction Medicine recognizes those who have successfully completed either exam as being certified in Canada.

A potential future direction may include family physicians working more in a collaborative care model. Collaborative care is defined as care provided by providers from different specialties, disciplines, or sectors working together to offer complementary services and mutual support. Over the last 10 years, a successful collaborative partnership between primary care and mental health care providers has resulted in improved access to mental health care as well as an enhanced capacity of primary care to manage mental health problems (Kates et al. 2011). While there is no single collaborative model or style of practice, ingredients of a successful initiative include personal contacts; mutual respect,

trust, and recognition of each partner's contribution; evidence- and experienced-based practices; and responsiveness to changing needs and relevance to local resources availability, interests, and culture. In order to be successful, roles in the collaborative system need to be delineated. In its application to the management of patients with the continuum of substance use and behaviors, from at risk use to addiction, a collaborative model may best allow for flexibility in care options able to be provided to patients depending on their severity, complexity, and other needs.

142.2 Generalist and Specialist Training

142.2.1 Family Physician Training

Canada has one of the strongest primary care systems in the developed world. Family physicians represent the primary gatekeepers to the delivery of medical services in all Canadian settings. Previously, some jurisdictions allowed physicians to practice as primary care physicians with only 1 year of postgraduate training, but now, the only route to practice eligibility is through a 2-year postgraduate residency in family medicine, followed by a certification exam, before practice eligibility. Residents in any 1 of the 14 programs accredited by the CFPC are trained to provide comprehensive and continuing care across the life span where the family physician is expected to be a skilled clinician with expertise in managing common problems in the community, ranging from acute, simple conditions to more complex biopsychosocial problems. Although the management of addiction (including screening, identification, motivation, treatment, and referral along with medical care and long-term follow-up) likely should represent a core aspect of all family physician practices, many do not address addiction and related disorders in their patients. There appear to be a number of practice-based factors contributing to this. First off, most provinces do not fully compensate family physicians for addiction or other types of counseling via the publically funded fee-for-service system. Visits to the family physician office then tend to focus on medical consequences of addiction rather than treatment of the addiction. If counseling is desired, typically patients are then referred to nonphysician services either within their practices, but more commonly outside, often resulting in a lack of continuity in service provision or loss to follow-up. Screening is also not entrenched in typical practice patterns to help identify patients without overt consequences of addiction. Adding to this, provincial and territorial drug plans typically do not cover many medications used to treat addiction (e.g., buprenorphine, naltrexone, acamprosate), further limiting visits to medical consequences of addiction, rather than addressing their causes.

Beyond practice-related issues, to date the CFPC has also not instituted a set curriculum in addictions, and few academic family physicians have expertise in addiction, making them reluctant to address addiction issues in seminars or clinical supervision. For example, in a qualitative study, a sample of Ontario's medical faculty admitted that they did not know how to intervene with addicted patients and were unsure if addiction interventions would make a difference (Midmer et al. 2002).

In another qualitative study, Ontario medical students reported that supervising staff rarely addressed the patient's addiction during encounters with addicted patients (Midmer et al. 2008).

Recognizing the deficits, the CFPC has attempted to target residency training in addiction a priority topic based on a 1998 needs assessment survey of Canadian family medicine faculty (Working Group on the Certification Process 2009). In the survey, faculty members were asked to identify which clinical topics residents must be competent in upon graduation. Sixty percent listed substance abuse as a priority, placing it third highest on a list of 100, ahead of ischemic heart disease, diabetes, and hypertension. For each priority topic, the CFPC has developed a list of evaluation objectives, which can be included on the CFPC national certification exam. For addiction and related disorders, the evaluation objectives focus on screening and are listed in Table 142.1.

Further components that likely will need to be added to would also include skills in performing brief interventions (especially for tobacco and alcohol as these represent over two thirds of the substance-related costs to Canadian society annually (Rehm et al. 2007)), recognition of at risk individuals for developing prescription opioid and benzodiazepine dependence, patient placement decision making for detoxification or treatment, and how to refer for treatment when beyond the scope of a family physician. Specific competencies will need to be defined to accompany the evaluation objectives and targeted recommendations, and accreditation by the CFPC of the 14 individual family medicine residency programs will need to become contingent upon their implementation to promote a common curriculum or national curricular mapping. Potentially, the grid included to describe psychiatry training could be applied to family physician training as found in Table 142.3.

As a common curriculum is not yet present, family physicians that have developed more focused addiction medicine practices typically have done so by pursuing education in addiction medicine through self-learning or continuing medical

Table 142.1 CFPC Evaluation Objective and Target Recommendations

Evaluation objective:
For all patients, especially high-risk groups (e.g.: mental illness, chronic disability), screen for the presence of a substance use disorder (tobacco, alcohol, illicit drugs)
Target recommendations:
Screen for blood-borne illnesses (e.g., human immunodeficiency virus, hepatitis) and offer relevant vaccinations or initiate treatments/referrals in patients with intravenous drug use
Diagnose and manage substance-induced intoxication and withdrawal syndromes
Discuss substance use with adolescents and their caregivers when warning signs are present (e.g., school failure, behavior change)
Consider and look for substance use disorders as a possible contributing factor when presenting problems fail to respond to appropriate initial interventions
Offer support to patients and family members affected by substance use disorders
Determine if a patient identifies with a diagnosis of a substance use disorder, elicit willingness to abstain or reduce use, and screen for comorbidities (e.g., sexually transmitted infections, mental illness) or long-term complications (e.g., cirrhosis)

education (CME) primarily, with the minority seeking formal postgraduate training in addiction medicine. Only two centers in Canada currently provide fellowship training in addiction medicine for family physicians. They are flexible programs that provide an opportunity to train in settings with a wide range of clinical services devoted to addiction care.

It is hoped that addiction medicine will in time become a formal part of the curriculum in family physician training over time. As a step towards this, the CFPC has introduced a section of family physicians with special interests or focused practices where addiction medicine has received approval to form a working group to develop a program within this section. The process that follows opens opportunities to develop and ensure guidelines for family physician post graduate education, training, and practice in addiction medicine. Hopefully then, one of the strongest primary care systems in the developed world will be further improved to provide more consistent and comprehensive care for patients with addictions and related disorders.

142.2.2 Psychiatry Training

Specialist training in psychiatry in Canada involves 5 years of training where components depend on the postgraduate year (PGY) training level of the resident. In PGY-1, residents complete basic clinical training that is meant to encompass a broad medical experience relevant to their future practice in that subspecialty. For psychiatry, this includes exposure to family practice, psychiatry, emergency medicine, internal medicine/neurology, and pediatrics primarily but can also include exposure to general surgery, intensive care, and obstetrics and gynecology. In PGY 2 and 3, residents complete foundational training in core components of the specialty. For psychiatry, this includes rotations in child and adolescent, adult, and geriatric psychiatry in both inpatient and outpatient settings. In PGY 4 and 5, consultation skills in complex care patients are further emphasized with elective and selective rotations to further develop areas of subspecialty skill while maintaining generalist competencies. Across the 5 years, psychotherapy training in at least three modalities is expected (typically psychodynamic, cognitive behavioral, and group/family as the core) as well as care of patients with chronic and persistent mental illness. Formal subspecialty designation extends training one more year (PGY-6), for a total of 6 years, if residents are seeking designations in one of the three RCPSC recognized subspecialties: child and adolescent, geriatric, or forensic psychiatry.

In 1997, the initial Curriculum Guidelines for Residency Training of Psychiatrists in Substance-Related Disorders was published by the Canadian Psychiatric Association (CPA) as a position paper (el-Guebaly and Garneau 1997). The stated goals of those guidelines were to:

- improve the knowledge, skills, and attitudes of psychiatrists about substance-related disorders to a level comparable to other mental disorders;
- ensure better evaluation and treatment of alcohol and other substance abusers;

- foster recognition of the impact of co-morbid substance abuse on the treatment and evolution of other physical and psychiatric conditions;
- prevent marginalization and excessive demedicalization of clinical services to substance abusers;
- ensure that psychiatrists develop an understanding of the spectrum of health care systems providing services to substance abusers; and
- foster advanced training and subspecialization of a greater number of psychiatrists to develop clinical services, teaching, and research in substance abuse.

However, without the 1997 proposed Curriculum Guidelines being directly incorporated into the RCPSC Specialty Training Requirements (STR) in psychiatry, curriculum changes were left up to individual programs to voluntarily implement, and relatively little change occurred.

In 2000, the RCPSC adopted minimum expected competencies in each of seven roles to be achieved by the end of training of a specialist revolving around the central role of the medical expert, including professional, scholar, communicator, manager, collaborator, and health advocate (Frank et al. 1996). The framework called the "CanMEDS roles" is derived from the "Canadian Medical Education Directions for Specialists" and forms the basis for educational standards for the Royal College. It has been incorporated into residency training accreditation and evaluation, examinations, individual specialty Objectives of Training (OTR), and standards for continuing professional development.

To attempt to begin to address the training deficiency in addictions, in 2007 the RCPSC released the new STR in psychiatry outlining more specifically expectations in training for psychiatry residents in addiction. Psychiatry is the first specialty in Canada to include specific training expectations in addiction. While the Objectives of Training (OTR) in psychiatry mentions alcohol and other substance use disorders, it does not currently include pathological gambling or potentially other research criteria behavioral addictions (e.g., Internet use gaming disorder), which would be recommended to reflect the changes in DSM-5 terminology and trends in addiction treatments. Proficiencies in addictions and related disorders are now part of the training requirements for all Canadian psychiatry residents who began their training as of July 1, 2009, to be realized over the 5 years of residency training with there being no less than the equivalent of a 1-month clinical experience evaluated separately from other rotations occurring sometime during PGY 2–5. Although it is unlikely that a 1-month experience would fully allow the resident to fully realize the proficiencies expected in the OTR/STR, the 1-month experience coupled with seminars should provide an adequate foundation for residents in addiction and related disorders that can be further built upon via additional training experiences and ongoing continuing medical education.

The OTR/STR as they apply to training in addiction include the following:

1. Supervised experience in the treatment of patients with addictions in a variety of settings. A learning portfolio or log should be maintained and reviewed by the program director. This experience must be undertaken as a discrete rotation of no less than 1 month or incorporated as a longitudinal experience (at any time during PGY 2–5) of no less than the equivalent of 1 month. This must be documented and evaluated separately from other rotations.

2. Availability of a selective rotation in addictions of no less than 3 months but preferably 6 months during senior psychiatric residency training (PGY 4–5) to develop advanced knowledge (see definition in Table 142.2) in addiction psychiatry.
3. Proficient (see definition in Table 142.2) clinical knowledge, skills, and attitudes appropriate to their practice in addiction.
4. Function effectively as consultants, integrating all of the CanMEDS roles to provide optimal, ethical, and patient-centered medical care by identifying and appropriately responding to those patients with addiction comorbidity.
5. Demonstrate introductory (see definition in Table 142.2) knowledge in assessing suitability for prescribing and delivery of motivational interviewing.

Table 142.2 Definitions

Introductory knowledge: able to recognize, identify, or describe principles
Working knowledge: able to demonstrate core aspects of psychiatry, such as basic interviewing, problem formulation, and treatment. The resident can understand the scientific literature
Proficient: able to demonstrate working knowledge enhanced by a developmental, cultural, and life span perspective, allowing detailed interviewing and biopsychosocial problem formulation with capacity to teach, consult, assess, and manage referrals. The resident can critically review and apply the scientific literature relevant to this competency
Advanced: detailed and sophisticated understanding which is multimodal and interdisciplinary, leading to advanced teaching and consultation on complex referrals. The resident has a detailed knowledge of and is able to apply the scientific literature, adapting and extrapolating as required

Table 142.3 Proposed stage-specific competencies in addictions and related disorders

		PGY-1	PGY-2/3	PGY-4/5[a]
Knowledge	Substance effects	WK	Prof.	Adv.
	Biopsychosocial understanding	WK	Prof.	Adv.
	Epidemiology	Intro	WK	Prof/Adv.
	Community resources	Intro	WK	Prof/Adv.
Skills	Screening	WK	Prof.	Adv.
	Assessment and diagnosis	WK	Prof.	Adv.
	Management of intoxication/withdrawal	WK	Prof.	Adv.
	Patient placement	Intro	WK	Prof/Adv.
	Pharmacotherapy	Intro	WK	Prof/Adv.
	Psychotherapy			
	Brief interventions	WK	Prof.	Adv.
	MI	Intro	WK	Prof/Adv.
	CBT/relapse prevention	Intro	WK	Prof/Adv.
	TSF and contingency mgt	Intro	WK	Prof/Adv.
	Family	Intro	WK	Prof/Adv.

Intro introductory knowledge, *WK* working knowledge, *Prof* proficient, *Adv* advanced
[a]Psychiatry 3–6-month selective training

Based on program and resident-derived factors, each training program will need to determine the optimal positioning of the clinical rotation in addictions. The flexibility in the timing and duration of the addiction rotation, however, could lead to significant variability in the foundational knowledge and skills that each resident would possess at that time in their training, a factor that would need to be considered by program directors when establishing rotations. Junior residents may be more proficient in the medical management of intoxication and withdrawal states but less proficient in assessment, diagnostic, and psychotherapeutic practices for these chronic disorders, potentially limiting the impact of early addiction training experiences on future psychiatric practice. Positive experiences in earlier training though may set the stage for psychiatry residents to seek out selective rotations in addiction psychiatry in their senior training years, helping to establish future leaders in addiction psychiatry. Senior residents may benefit more from addiction training experiences given their greater exposure to psychotherapy training, enhanced assessment skills, and likely better established future practice plans, allowing them to better focus learning to those areas most applicable to their future practices (e.g., screening and brief intervention skills for consultation-liaison psychiatrists, motivational interviewing and other engagement skills for inpatient psychiatrists, or use of evidence-based harm reduction approaches for assertive community treatment team psychiatrists working with chronic psychotic disorders), but residency training programs may have greater difficulty integrating these experiences in the senior years due to limited availability of concurrent psychiatric and addictive disorder training centers and limited access to primary addiction services. Longitudinal experiences may bridge this divide but may also be difficult to ensure a consistent training experience involving addiction psychiatry role models and evidence-based practices. To ensure appropriate evaluation and oversight, all training programs will need to appoint a training coordinator for this endeavor who ideally would already be certified in addiction medicine or addiction psychiatry or have completed a fellowship in addiction psychiatry.

The goal of the new OTR/STR was not only to provide a template for training the "sophisticated generalist" in contemporary psychiatric practice but also to provide a potential template for psychiatric subspecialization and its recognition (Leverette 2009). In 2011, the RCPSC drafted a series of white papers, including one on specialization (Royal College of Physicians and Surgeons of Canada. Generalism: achieving a balance with specialization. Draft: January 31 2011). The white paper recognizes that "the areas of focus and competence (diplomas) are one method to encourage physicians to learn new skills to adapt to community needs." In 2002, the RCPSC adopted the following definition (Committee on Specialties (COS) 2002): "A subspecialty is defined as having a body of knowledge and identifiable competencies that build upon the broad-based body of knowledge defined as a specialty. There must be evidence of societal need for the subspecialty to justify development and support for an RCPSC-accredited training program. Successful completion of a subspecialty requires certification by examination in one of the primary specialties and successful completion of a subspecialty-training program. Subspecialty training must be at least one year in duration, can only be entered in the final year of

primary specialty training, and may be evaluated with or without a RCPSC examination." Increasing demands to recognize more and more subspecialities has led the RCPSC to develop an innovative diploma category where the more formal and rigorous standards attached to subspecialty recognition do not have to be met. Diploma recognition will be based on 1 year of training establishing and educational portfolio instead of an examination. This initial step may help gauge interest in addiction psychiatry in Canada, better establish manpower needs, and better standardize the content for fellowship training in addiction psychiatry. The downside of this is that the focus on psychiatry in those examinations is more limited in nature, there is no commensurate change in remuneration for completing certification, and physicians can still choose to practice in the field without certification. With the number of experienced faculty in addiction psychiatry in Canada at present being relatively limited, a tenuous balance needs to be maintained between moving towards subspecialty recognition for addiction psychiatry without dissuading potential interested psychiatrists from pursuing additional training. Ideally, the year of subspecialty training could occur within the current 5-year residency training or, likely, with a fellowship year.

In Canada, there currently is no defined subspecialty of addiction psychiatry, like there is recognized by the American Boards in the United States. While fellowships in addiction psychiatry are available in Canada, their content and expectations varies from institution to institution with only a minority of training programs being able to provide fellowship training. The OTR/STR for addictions describes that a selective (or elective) in addiction psychiatry or addiction medicine of 3 months to a year in duration be available to senior psychiatry residents (PGY-4/5) to developed advanced knowledge in addiction psychiatry. Currently, few programs have this capability in Canada, but this may allow the better identification of Canadian training sites with the capacity and facilitate fellowship/diploma development at those identified sites.

The OTR/STR for addictions has a number of deficits or weaknesses. Residents will only be required to have an introductory knowledge (ability to recognize, identify, or describe principles) of motivational interviewing (MI), even though the ability to provide MI and integrate it into day-to-day practice is typically viewed as a core component of addiction psychiatry (Crockford and el-Guebaly 2009; Renner et al. 2005). The OTR/STR also fails to identify the other core psychotherapeutic approaches utilized in standard addiction psychiatry practice including cognitive behavioral therapy (CBT)/relapse prevention and 12-step facilitation.

It is recommended that clinical knowledge, skills, and attitudes in addiction involve the following domains:

1. ***Substance Effects*:**
   (A) Knowledge of the mechanism of action for the primary drugs of abuse and dependence including alcohol, nicotine/tobacco, caffeine, cannabis, sedative-hypnotics (benzodiazepines, barbiturates, GHB), stimulants (cocaine, amphetamines, and "designer" stimulants), opiates, NMDA antagonists (PCP and ketamine), inhalants, steroids, and hallucinogens

(classical and "designer" hallucinogens). This would represent a foundation to understanding how substance dependence develops and the basis for different intoxication/withdrawal syndromes.

(B) Knowledge of substance intoxication/withdrawal syndromes enabling their identification and acute management.

(C) Knowledge of the effects of chronic substance use on the development and perpetuation of medical complications (e.g., hepatitis, HIV) and psychiatric comorbidity.

(D) Awareness of the similarities and differences between behavioral and substance-related addictions.

2. ***Developing a biopsychosocial understanding of addiction and their overlap with major psychiatric disorders*:**

(A) Knowledge of the critical role of the brain's extended dopamine reward pathway as the key mediator of the neurobiological basis for how addiction develop incentive salience for future behavior choice over natural rewards, balanced with the understanding of other biopsychosocial factors contributing to risk and resilience including drug type, delivery method, dosing, age of exposure, genetics, underlying psychiatric disorders and personality traits, expectancies from use, environment, peer use, availability, cultural/religious factors, and economics.

(B) Awareness of how initial psychosocial factors contribute to the initial exposure to addictive substances and behaviors, then progress to having a more biologic and chronic basis once addiction develops. The same would help frame the basis for choosing different strategies to address the continuum of addiction behavior from at risk use to the most severe forms of addiction.

(C) Understanding of how common comorbid psychiatric disorders have overlapping neurobiological and psychosocial contributors contributing to the development and perpetuation of addiction.

3. ***Addiction Epidemiology*:**

(A) Knowledge of the prevalence of each of the addiction and the differences between populations based on age, location, and ethnicity.

(B) Knowledge of the comorbidity with the spectrum of major psychiatric (including mood, anxiety, psychotic, cognitive, sleep, attention deficit hyperactivity, personality, and somatic/pain disorders) and medical disorders.

(C) Knowledge of developing trends in addiction related to availability, perception of harm, and other factors that promote and protect their development.

(D) Awareness of the different trajectories and predictors for the course of addiction. Understanding how access to evidence-based treatments can change outcomes and awareness of the phenomenon of natural recovery, to help build appropriate optimism for change.

4. ***Assessment and Diagnosis*:**

(A) Knowledge and skills in the identification of addiction and their diagnostic definitions. This would include knowing how to elicit history

indicative of addiction and related disorders, awareness of typical signs and symptoms that would prompt more in depth screening, and the importance of screening for tobacco use, prescription drugs, over-the-counter medications, and behavioral addictions in addition to alcohol and illicit drugs.

(B) Familiarity with the use of screening instruments for substance use disorders (e.g., CAGE, Alcohol Use Disorders Identification Test (AUDIT) for alcohol, Drug Abuse Screening Test (DAST) for drugs) and their minimum cutoff values. Awareness of more comprehensive instruments to more thoroughly evaluate the impact of addictive behaviors (e.g., Addiction Severity Index). Familiarity with use of the Clinical Institute Withdrawal Assessment for Alcohol, Revised (CIWA-Ar).

(C) Awareness of the role of urine drug screening, other forms of drug screening, and their potential limitations.

(D) Knowledge and skills to attempt to reasonably differentiate substance-induced psychiatric symptoms from independent psychiatric disorders. Awareness of common comorbid conditions when one disorder is identified (e.g., problematic sexual behavior with stimulant addictions; anxiety, depressive, and sleep disorders with sedative-hypnotic dependence).

5. ***Stage of Change and Treatment Planning*:**

(A) Knowledge of the different stages of change reflective of the transtheoretical model and how it is assessed. Awareness that stage of change may change over time and may be different for each psychiatric and/or addictive disorder.

(B) Know how and when to use a brief intervention, motivational interviewing, cognitive behavioral therapy (CBT)/relapse prevention, or 12-step facilitation with awareness of contingency management as a method to create short-term incentives towards drug use reduction and abstinence.

(C) Understand what constitutes appropriate addiction treatment as it relates to setting (e.g., outpatient, residential, inpatient), minimum durations, and types of providers. Skills to select best treatments and modify these based on response (e.g., use of the American Society of Addiction Medicine Patient Placement Criteria (ASAM PPC-2R)).

(D) Knowledge and skill in the use of pharmacotherapy for addiction including those for alcohol withdrawal, opioid substitution, treatment of alcohol dependence (e.g., naltrexone, disulfiram, acamprosate) and nicotine dependence (e.g., nicotine replacement therapy, bupropion, varenicline), and tapering off of opioids and sedative-hypnotics.

(E) Knowledge and skills in the use of pharmacotherapy and psychotherapy for comorbid psychiatric and addictive disorders.

6. ***Community Resources*:**

(A) Knowledge of mutual help (e.g., Alcoholics Anonymous, Rational Recovery) and how to facilitate involvement in these resources (e.g., 12-step facilitation).

(B) Knowledge of the spectrum of other community resources available to help manage addictions and related disorders unique to their community including evidence-based harm reduction approaches, detoxification facilities, outpatient treatment options, and residential treatment centers.

7. ***Role of Family*:**
   (A) Knowledge of the impact of addiction on the addicted person's family and contacts.
   (B) Knowledge and skills to support and involve the person's family in the recovery process from psychoeducation to couples/family therapy.
8. ***Attitudes*:**
   (A) Awareness of potential biases held towards patients with addiction and development of empathy for their condition.
   (B) Development of appropriate optimism for change and improvement over time in persons with addiction while recognizing that addiction requires an approach reflective of a chronic disorder.

The recommended areas for clinical knowledge in addiction psychiatry in Canada are outlined in Table 142.3. Beyond clinical knowledge competencies, the curriculum in addiction psychiatry will need to emphasize one that is skills based and interactive/experiential in nature (both in seminar teaching and active patient care) to have meaningful impact on future practice patterns as well as recognize the lifelong process of learning building from medical school and reinforced through continuing medical education (CME).

142.3 Conclusion

Medical education in addiction is a work in progress in Canada, but promising developments may help shape standard setting for training in primary care and psychiatry. The challenge going forwards, for both family physicians and specialists, will be to build on the training requirements to broaden their impact. Opportunities for learners to experience collaborative care learning together and from each other further establish administrative structures and support experienced faculty in addiction medicine/psychiatry to train the next generation, establish/expand upon core knowledge and skill-based competencies ensconced in accreditation standards, and eventually develop capacity for subspecialty recognition through defined selective/fellowship training guidelines.

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Development of a Full Medical Specialty in Addiction Medicine: The Norwegian Experience

143

Gabrielle K. Welle-Strand

Contents

Abstract

In June 2012, the Norwegian Minister of Health and Care Services put forward a Governmental White Paper on "Drug and Alcohol Policy" which included the decision to establish a full medical speciality in addiction medicine. The Norwegian substance use problems are of typical European pattern. During the

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last 20 years, addiction treatment in Norway has developed from a nonmedical, social service-based approach to a comprehensive interdisciplinary service based on health laws for treatment and social service laws for rehabilitation. Increasing overdose mortality and the spread of HIV caused trial projects with methadone, and in 1997 a national program for substitution treatment was established. The specialized treatment service for drug- and alcohol-using patients is called interdisciplinary specialized treatment (IST). There has been increasing awareness of the physical and mental health condition of substance use patients and the rising morbidity and mortality. Both nationally and internationally, there has been an expansion of the knowledge base for addiction medicine.

The organization and responsibility for the education and approval of all medical specialties are also undergoing a major change to match future needs of the patients and a changing and modern society. The specialty in addiction medicine is in many ways an acid test for these changes.

Addiction medicine is a new specialty. It is 15 years since the last time a new medical specialty was launched in Norway. A broad process has been and is taking place in order to develop all necessary parts of the new specialty.

The suggested specialty regulations include 5 years of internship in accredited institutions:

1. 42 months of internship in interdisciplinary specialized treatment (IST), including 12 months in a detoxification department, 6 months in inpatient addiction treatment, and 12 months of outpatient addiction treatment. The last 12 months can be chosen from a range of services.
2. 18 months in other specialist areas: 6 months in a psychiatric ward. For the last 12 months, the candidate must choose two of the following: 6 months more of psychiatry, 6 months in a somatic ward, or 6 months in general practice.

The candidate must have 270 hours of coursework and regular clinical supervision and also 30 hours of specialized supervision in therapy related to addictions.

We also have developed a suggestion for interim regulations, to be able to approve the first specialists in addiction medicine in the autumn of 2014; they will be the mentors/supervisors for the new specialist candidates of addiction medicine. Hopefully the first candidates of this full specialty in addiction medicine will be in training from 2015 at the first accredited teaching institutions, to improve the quality and competence of the medical doctors in the substance use field for the benefit of our patients.

143.1 Introduction

Nothing less must be provided for the treatment of substance dependence than a qualified, systematic, science-based approach such as that developed to treat other chronic diseases considered untreatable some decades ago (World Health Organization 2004).

Norway is in some ways different from the rest of Europe, not being a part of the European Union, but nevertheless in most ways integrated in the European collaborations. The substance use problems are of typical European pattern, but there are some special traits of interest in relation to addiction treatment. Norway has five million inhabitants with some urban centers such as the capital Oslo with 550,000 inhabitants and cities such as Bergen (250,000), Trondheim (150,000), and Stavanger (100,000), but the degree of urbanizations is relatively low. Nevertheless, the addiction problems are on average European levels.

During the last two decades, drug and alcohol treatment in Norway has developed from a nonmedical, social service-based approach to a comprehensive, interdisciplinary service based on health laws for substance treatment and social service laws for the rehabilitation process. There has been increasing demand for evidence-based approach and research. In June 2012, the Norwegian Minister of Health and Care Services, Anne-Grete Strøm-Erichsen, put forward a Governmental White Paper on "Drug and Alcohol Policy" for the Norwegian parliament. One of the decisions in this paper was to establish a full medical speciality in addiction medicine. In this chapter we describe the core elements in the development and the plans for the medical specialty in addiction medicine.

143.2 The Medical Specialty Project

143.2.1 Drug and Alcohol Treatment in Norway: Past and Present

Until the turn of the century, addiction was largely seen as a social problem. Medical treatment and the disease model for addiction were to a large extent rejected. The treatment was organized within the social welfare system and based on social care laws. Health care was mainly considered when indicated by psychiatric or somatic comorbidity. Opioid maintenance treatment (OMT) for opioid-dependent patients was rejected. Increasing overdose mortality and the spread of HIV caused trial projects with methadone from 1991, and in 1997 the parliament decided on a national program for OMT.

During the same period, the health-care system underwent basic structural reforms. The system had been a centralized system basically planned and led by the ministries and directorates. Now Norway developed a system based on municipal social care and primary health services and local hospitals run by the four regional health enterprises. Further, new law reforms established a health-care system based on new health laws. This meant that municipal health and social care and specialized health-care services were structured with appointed municipal GPs and specialist services from health enterprises headed by the regional health authorities.

This development also necessitated changes in addiction treatment. So far, the addiction treatment had been organized on municipal level as a responsibility of the social welfare system and on regional level as a responsibility for the counties, also based on social care law systems.

The Drug and Alcohol Treatment Reform that was passed as a Law Amendment in the Norwegian Parliament in 2003 established addiction treatment as an interdisciplinary specialized treatment which became the responsibility of the regional health authorities. This "Drug Reform" laid the organizational foundation for expansion and improvement for the specialized services for patients with substance use problems. The introduction of patient's rights in the "Drug Reforms" was an important step for improving the treatment for substance-using patients. The focus has since then increasingly been put on patient involvement in the treatment process both on an individual and a general level. The "Drug Reform" has been evaluated to be successful as far as organization is concerned, but as lacking both in the quantity and quality of the treatment offered.

The specialized treatment services for drug- and alcohol-using patients is called interdisciplinary specialized treatment (IST), indicating the necessity for the involvement of different health and social welfare system professionals in the treatment, even though the treatment is organized under the health-care system. The government has been giving priority to drug and alcohol treatment and psychiatric treatment in the budgets for hospital funding for some years. There has been a general expansion in the treatment capacity for interdisciplinary specialized treatment since 2004, but there are still too few treatment slots for both in- and outpatient treatment. As in other countries, the expansion has primarily been for outpatient services.

In the municipalities the social welfare system still has the main responsibility for the follow-up and rehabilitation for substance use patients, but general practitioners have been given a more important role in substance treatment than previously. The continuity of the services and the smooth cooperation between the social welfare system, the general practitioners, and the specialized treatment system has "always" been and still is one of the greatest challenges in substance treatment systems.

In October 2007, as part of its budget proposal, the government presented an action plan for the drug and alcohol field for 2007–2012. The plan ranged from prevention to treatment and rehabilitation. The aim of the plan was a policy with a clear public health perspective. The aim was also to raise professional standards through research and strengthening competence and quality. The five main goals of the action plan were:

1. A clear public health perspective
2. Better quality and increased competence
3. More accessible services and increased social inclusion
4. Binding cooperation
5. Increased user influence and greater attention to the interest of children and family members

In 2010 "the Coordination Reform" was amended by the Norwegian parliament. The goal of this reform is for the patient to receive the proper treatment – at the right place and right time. It is stated that the patients' needs for coordinated services are

not being sufficiently met. The reform presumes that the municipalities will play the largest part in meeting growth in demand for health services.

143.2.2 Patient Population

The total alcohol consumption in 2012 was estimated to be approximately 6.2 litres of alcohol per inhabitant over 15 years of age (1995: 5.4 litres). The estimate for high alcohol consumption from the National Institute for Drug and Alcohol Research (SIRUS, the Norwegian abbreviation) in 2006 was between 66,000 and 122,000 persons in Norway (Bretteville-Jensen and Amundsen 2006).

Two surveys on drug use among young people in 2006, one among the 15–20 age group and one among young adults aged 21–30, showed major differences (Skretting 2007; Lund et al. 2007). The percentage of 15–20-year-olds ever having used cannabis was 13 %, whereas 34 % of the 21–30-year-olds reported cannabis use. For people under 20 years, lifetime prevalence of amphetamine, cocaine, and ecstasy has declined from 1998 to 2006. For the young adults, 21–30 years of age, the lifetime prevalence for all three drugs has increased considerably. Cocaine was reported to have ever been used by 2.2 % of the 15–20-year-olds in 2006, while 9 % of the 21–30-year-olds reported the same. Concerning amphetamines, 3.1 % of the 15–20-year-olds reported use, whereas 9 % of the 21–30-year-olds. SIRUS estimated in 2005 that there were between 8,200 and 12,500 injecting drug users in Norway (Bretteville-Jensen and Amundsen 2006).

The number of HIV cases among injecting drug users remains low in Norway, and the yearly incidence has been low for the last 15 years. The prevalence rate even in the most affected groups in Oslo is less than 5 %. The HIV-testing rate is high, and there are very few undetected HIV cases when AIDS is diagnosed. There has been a hepatitis B outbreak among injecting drug users during recent years. During the period 1995–2006, the total number of reported cases of acute hepatitis B among drug users was 1,812. The infection rate of hepatitis C among injecting drug users is high, ranging from 60 % to 90 % prevalence in different tested populations throughout the country. The degree of comorbidity concerning both somatic and psychiatric illness is high among both drug- and alcohol-dependent patients.

Drug overdose deaths rose from the mid-1990s until 2001 (338 people that year), and thereafter there has been a decline. In the years 2006–2010, between 200 and 250 persons died each year as a result of opiate overdose. This puts Norway among the three countries with highest incidence of opioid overdose deaths in Europe (Mortality related to drug use in Europe 2011) even though figures are not directly comparable from country to country due to differences in registration and autopsy practices.

In 2011 there were 1,753 inpatient treatment slots in interdisciplinary specialized treatment (IST) and approximately 300,000 outpatient consultations in IST. There

were 7,000 patients in opioid maintenance treatment (OMT) at the end of 2012, estimated to be more than 50 % of the target population. Half of the patients were treated with methadone and the other half with buprenorphine.

143.2.3 Development of the Addiction Field in Recent Years

There has been increasing awareness of the health condition of substance use patients and their rising morbidity and mortality. Both nationally and internationally, there has been an expansion of the knowledge base for addiction medicine, including better treatment possibilities. Research on substance use patients has increased in Norway. In addition to the existing institutions performing research in the drug and alcohol field, the Norwegian Centre for Addiction Research (SERAF, Norwegian abbreviation) at the University of Oslo was established after an initiative from the Norwegian government in 2007 (Bramness et al. 2011).

The development of national treatment guidelines, headed by the Norwegian Directorate of Health, has been given high priority. A national treatment guideline for opioid maintenance treatment (OMT) was published in 2010 (Norwegian Directorate of Health 2010), a national treatment guideline for pregnant women in OMT and the follow-up of the children and their families until school age was published in 2011 (Welle-Strand and Bakstad 2011), and also in 2011, a national treatment guideline for the diagnosis, treatment, and the follow-up of persons with both substance use disorders and psychiatric disorders was published (Norwegian Directorate of Health 2011). A national guideline for detoxification and another for treatment of substance use patients will be finalized in 2014 and 2015, respectively.

143.2.4 A Full Medical Specialty in Addiction Medicine

As described above, the development in Norway has brought an increasing emphasis on health-care treatment systems for addiction. Interdisciplinary specialized treatment has been placed at the core of the services. This means that substance treatment is organized based on specialized hospital units. In contrast to other areas, however, specialized medical competencies have been lacking in the addiction treatment. There are 44 recognized medical specialties in Norway, of which eight are subspecialties in internal medicine and five are subspecialties in general surgery. The majority of these are linked to specialist health care, but there are also specialties in primary health care, family medicine, community medicine, and occupational medicine. There is one physician for every 278 people in Norway. More than half of Norway's 18,000 active physicians are qualified as specialists, and most of the other physicians are in specialist training to become specialists. To be appointed to a senior medical post, specialist approval is a minimum requirement.

The situation is somewhat different for the specialist services for addiction – the IST. The Norwegian Directorate of Health performed a survey of medical doctors

working in IST both in 2009 and in 2011. Putting together the results, a total of 132 positions for medical doctors were identified within IST, and 12 % of the positions were vacant. Of specialists working in the IST services, at least 32 psychiatrists, 14 general practitioners, and 13 doctors with other specialties were identified. The numbers are not complete, while some hospitals did not send in their records. The Norwegian Association of Addiction Medicine (NFRAM, Norwegian abbreviation) analyzed the situation and suggested that the need was a total of 400–450 medical doctors in IST, with half of them being specialists and the other half being doctors in training for a specialty.

For each medical specialty, there exists a specialty committee which has up to recently been responsible for the content of the training and for the accreditation of hospitals for graduate medical education. The 44 medical societies (associations of physicians with shared professional interests) work in close contact with relevant specialty committees and have up till now provided the hospital courses required for each specialty.

To become a medical specialist, a minimum of 3–4 years of residency in the main subject is required. For most specialties, 1 year in a subsidiary subject has also been required. A certain amount of coursework is required, on average 200 h. There are also specific requirements in relation to skills and procedures which have to be documented by attestation, checklists, and so on. The national courses have up to now been organized by the NMA (Norwegian Medical Association) in cooperation with the four Norwegian medical schools; there are approximately 350 courses each year in the 44 specialties.

Hospitals eligible for training specialists have to be approved. The criteria evaluated are staffing, patients, equipment, diagnostics and therapeutic procedures, and training plans, including plans for the tutorials. A tutor or a supervisor must be assigned to each resident. Approved training institutions are evaluated annually by reports on their teaching activities.

143.2.5 The Planning and Development of a New Specialty

A specialty in addiction medicine was initially proposed in 1999. It was turned down by the Norwegian Medical Association (NMA) arguing that GPs or other specialists, as, for instance, psychiatrists or internists, should deal with a patient's addiction problems. The second proposal from the Norwegian Association of Addiction Medicine (NFRAM) was considered positive by the NMA but was turned down in 2003 by the Norwegian Council for Specialities and Specialist Education. The reason for the rejection was once again that other specialities could deal with addiction problems and also that it would be difficult to establish enough teaching institutions and proper guidance for the specialist candidates.

The proposal was actualized again when the "Drug Reform" was launched by the government giving the specialized health-care system the responsibility for the treatment of drug and alcohol patients. The interdisciplinary specialized treatment (IST) was established for the treatment of patients with problems with alcohol,

prescribed drugs, illegal drugs and other addictions. The situation was thus that we had a new medical speciality without specialist medical doctors. In 2008, the Norwegian Medical Association (NMA) made a general report describing the education of medical specialists in Norway compared to other European countries. In this process the question concerning a new specialty in addiction medicine was raised again.

NMA therefore asked NFRAM, which is one of the 60 specialty branches in the NMA (associations of physicians with shared scientific interests), to make an evaluation of a possible new speciality in addiction medicine. NFRAM concluded in its report that it was both feasible and appropriate to establish a new specialty in addiction medicine and recommended this be done (Strøm et al. 2008). This report was approved by the general assembly in NMA in June 2009. NMA subsequently sent a recommendation to the Ministry of Health and Care Services and to the Norwegian Directorate of Health to establish a full specialty in addiction medicine. The report was further developed and then approved by the Norwegian Council for Specialties and Specialist training and the Norwegian Directorate of Health in 2010. Finally, on 22 June 2012, the decision was announced by the Ministry of Health and Care Services. A full medical speciality in addiction medicine was now a reality.

A medical speciality is characterized by a defined set of medical problems and diseases not covered by other medical specialities: a specified theoretical base and knowledge base, specified techniques, and competence in examination and diagnosis related to this specialty.

143.2.6 The NMA Suggestion: Goals for Competence and Suggested Specialty Rules

Addiction medicine is related to problems due to the use of psychoactive substances and also includes the behavioral addictions such as gambling and Internet addiction. The patients' problems are usually due to biological, psychological, and social factors. The clinical scope of addiction medicine comprises prevention, examination, diagnostics, treatment, and rehabilitation. To cover these areas, special medical knowledge and skills are needed. The patient's treatment should be multidisciplinary and based upon close cooperation between doctors, psychologists, social workers, and other professions.

Addiction medicine has four main perspectives: clinical activity, prevention and information to the public about drugs and addiction, guidance to other specialists and to general practitioners, and research and further development of addiction medicine.

The responsibility for developing new specialties and the postgraduate education of medical specialists in Norway have been moved from the Norwegian Medical Association to the Norwegian Directorate of Health in recent years. The specialty in addiction medicine is the first specialty to be developed by the Directorate. The suggestion for the education in addiction medicine which was put forward prior to the decision of a full specialty in addiction medicine in 2012 was in line with the general rules which existed then.

143.2.7 New Changes in the Development of All Medical Specialties in Norway

The Norwegian Directorate of Health was in 2011 commissioned by the Ministry of Health to evaluate the present specialty structure and content for all medical specialties and to suggest changes which will improve the current system. Which medical specialties do we need based on the demography and medical and technological development and the recent law amendments? How should the structure of the specialty education be? Should there be a common trunk for all the specialties? And further, should there be a common competence platform for groups of specialties? What ought to be the content of the education? The Directorate was also asked to suggest how the future roles and responsibilities for the specialist education ideally should be.

The purpose of this evaluation and change is a specialty education which matches the patients' needs and specialty education which is in line with the future need for the patients and the health service system. The specialty education should be national, but at the same time in line with the EU requirements.

The draft with the suggested changes was sent to the Ministry of Health in June 2013 (Fremtidens legespesialister 2013). The suggested structure divides the specialty education into three parts:

1. Eighteen months comprised of 1 year of internship at a hospital and half a year in general practice in the municipalities should be common for all the specialty candidates.
2. One to three years of specialty education for groups of specialists naturally belonging together. The suggestion also implies that subspecialties no longer will exist.
3. Two to four years of internship for each main specialty separately.

The common competence for all specialties could include teaching in communication, leadership and development of organizations, cooperation and coordination, team work, and quality improvement.

The framework for the future education of all medical specialties in Norway is presently being further developed by the Norwegian Directorate of Health and other bodies. Probably it will take another 3–5 years before the new system will be put into action.

The process of developing a new specialty in addiction medicine must be faster than the above process, and our first goal is therefore to make a kind of hybrid specialty: We will base the new specialty in addiction medicine on the present regulations for medical specialties, but at the same time we will be looking into the future and incorporate some of the probable future changes described in the document for future medical education in Norway (Fremtidens legespesialister 2013).

143.2.8 The Process of Establishing the Specialty in Addiction Medicine

Our aim has been to have a broad process with the involvement of all necessary parties in the process leading to a full medical specialty in addiction medicine.

At the same time we want to establish the new specialty rather fast, knowing that many of the present "specialists" in addiction medicine are aging and we need their competence to teach the future specialists.

In January 2013 we established an external committee with representation from all the involved parties: medical doctors working in addiction medicine in the four regional health enterprises, the municipalities, the Norwegian Medical Association, the other professions working in the field of addiction (psychologists, social workers), and service user's representatives. We also invited the members of the newly established specialty committee in addiction medicine in NMA into the work. At the same time we established an internal committee in the Norwegian Directorate of Health with representation from the relevant departments involved in medical education. Both committees have been working on further development of the specialty regulations for addiction medicine and other requirements for the new specialty. The regulations are based on the existing regulations for medical specialist education, but are at the same time taking into account the suggested changes for the future. We have also visited all the possible training hospitals, a total of 14 different hospitals around Norway. At the hospitals we have met a broad representation of professionals involved in addiction medicine and professional training in general, as well as the administration of the hospitals. As many of the interdisciplinary specialized treatment clinics are run by NGOs, they were also invited to the local meetings.

We have developed suggestions for both the specialist education regulations and for the interim regulations, to be able to approve the first specialists in addiction medicine. One large summit meeting has been arranged to ensure that the suggested rules and structure for the specialty in addiction medicine are well known in the relevant areas of medicine and that professionals have had a saying in the shaping of this new specialty. We have also performed a short written summit after the summit meeting. The suggested specialist and interim educational regulations will be sent to the Ministry of Health after an external review, which is responsible for the formal approval of the set of regulations.

143.2.9 The Framework for the New Specialty

The specialists in addiction medicine must have knowledge and skills in alcohol and legal and illegal drugs of abuse, other addictions, pharmacology, somatic and mental comorbidity, psychosocial conditions, prevention, treatment and rehabilitation, collaboration and cooperation, legislation, research, evaluation, and quality standards. Other areas in which the addiction medicine specialists need competence are substance use and pregnancy, addiction among young and elderly people, and other cultural subpopulations with addiction problems.

The structure for the internship after the 18 months of internship required for all doctors after medical school is as follows:

1. Five years of internship in accredited institutions.
   (a) Forty-two months of the internship should be in IST, including 1 year in a hospital department for detoxification/acute ward for drug and alcohol

patients, 6 months in an inpatient ward for substance use treatment, and 12 months in a department for outpatient addiction treatment, including practice with opioid maintenance treatment (OMT). The last 12 months of IST internship can be chosen from the following: more internship in any of the abovementioned departments, up to 6 months in municipality treatment for drug and alcohol (low-threshold health services, OMT at municipality level, prison health service, etc.) or addiction medicine Research.

(b) Eighteen months should be in other specialty areas: 6 months in psychiatry (acute ward, general psychiatry ward), and for the last 12 months, the candidate has to choose two of the following: 6 months of psychiatry (any part, including child and youth psychiatry), 6 months in a somatic ward (internal medicine, emergency ward, infectious disease ward, pharmacology, neurology, pediatrics, gynecology/obstetrics), or 6 months as a general practitioner.

All the internship has to be in accredited institution supervised by a specialist. There is a possibility of combining clinical work with addiction medicine research.

The candidate must have a total of 270 hours of compulsory coursework in defined areas of addiction medicine and other subjects.

The candidate must receive regular clinical supervision from a senior addiction medicine specialist, 1 hour per week, and have 30 hours of systematically specialized supervision in therapy related to addictions. Further, the candidates should have individualized learning plans which are evaluated every 6 months and which describe the candidate's skills and development in addiction medicine.

143.2.10 Why Did We Succeed to Get a Full Specialty in Addiction Medicine?

This has been a long struggle for Norwegian doctors involved in the treatment of addictions. We reached our goal and the decision to establish an addiction medicine specialty because of the steady and systematic work of many engaged doctors working with these patients who never gave up. The "Drug Reform" in 2004 was an important milestone and so was the strong support from the Norwegian Medical Association. The NFRAM report was solid, and the arguments for establishing a specialty in addiction medicine were based on evidence and understood by the other specialist associations in NMA. General practitioners, the psychiatrists, and the internists all supported the proposal. The Coordination Reform which was launched in 2012 relies on the support the specialized health-care system can give to the primary health care. This means that the doctors in the specialized health care (IST) must have expert's skills and knowledge about addiction medicine.

143.2.11 The Way Forward

Addiction medicine is a new specialty. Our goal is to have the first new specialist candidates in training in at least four hospitals from 2015.

As soon as the specialty and interim regulations are approved by the Ministry of Health, the Norwegian Directorate can receive applications from the medical doctors applying to be addiction medicine specialists after the interim regulations. These medical doctors have the necessary competence in addiction medicine to ensure clinical supervision for the new specialist candidates. They will be given a compulsory "crash course" focusing and central issues in addiction medicine and on how the training for the new addiction medicine specialists should be run.

When the first addiction medicine specialists are approved, their hospitals can apply to the Directorate to be appointed and accredited teaching institutions. We also have to develop assessment standards for the specialist candidates.

We are also in the process of establishing necessary structures to develop the necessary coursework for the new specialty.

143.2.12 Is the Norwegian Experience Applicable in Other Countries?

The development in addiction treatment has been quite different in countries around the world. This means that each country has to take steps forward at a pace and in a direction which is in line with both the health service in general and the treatment services for substance users in each particular country.

In Norway we are looking very much forward to establishing the new specialty in addiction medicine, and we are sure that this will represent a major step forward in improving the medical quality of the treatment services for substance use patients.

Norway is happy to share the experiences on developing a full specialty in addiction medicine, both the steps we have made up till now and those of the future, for the benefit of patients and professionals in other countries. This can surely be done through international organizations in addiction medicine as ISAM where we are about to build up a database focusing on what kind of systems for postgraduate training in addiction medicine exist in different countries around the world. In January 2014, ISAM has a network of approximately 30 national contacts from different countries on all five continents. ISAM also have the information about postgraduate training in addiction medicine in 25 of these countries. The database will also have contact information to both national and international Addiction Medicine Associations.

143.3 Conclusion

Addiction medicine is decided to be a full medical specialty in Norway. We have come a long way in the development of the new specialty, but there is still a lot of work ahead. We are happy to go on with this work for the benefit of our patients. It is axiomatic that more competent doctors mean better treatment for our patients.

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The Development of a National Training Program on Addiction Medicine in Indonesia

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Contents

Abstract

In Indonesia, substance use and misuse are a major public health concern with several problems, such as a huge prevalence of drug users, a small number of addiction treatment facilities, low utilization rate of treatment facilities, limited capacity of health professionals in addiction treatment field, and ongoing stigmatization. Addiction has been criminalized for a long time and has not

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been regarded yet as a medical problem. Addiction medicine is not recognized as a medical (sub)specialty. Most of the professionals working in addiction care have never received training on addiction. Medical education only provides addiction medicine training as a one-hour lecture as one of the psychiatric topics for medical students at the preclinical level. There is no formal training in addiction medicine for graduated medical doctors.

The Bandung Addiction Working Group developed as a part of the IMPACT program (Integrated Management of Prevention and Control and Treatment of HIV/AIDS) and in collaboration with several national and international institutions a national addiction medicine training program. They organize an expert consensus meeting of selected Indonesian experts in the field of addiction medicine. The meeting was followed by a training needs assessment and the curriculum development workshop. Those processes continued with the development of a national Indonesian Short Course in Addiction Medicine (I-SCAN). The kickoff I-SCAN training, planned for January 2012, was postponed. Lessons learned conclude this chapter.

144.1 Introduction

In Indonesia, substance use and misuse are a major public health concern. The National Narcotics Board estimated in 2008 that there were 3.3 million (1.99 %) drug users in Indonesia, including 1,580,384 (47 %) drug-addicted patients and 237,057 (15 %) injecting drug users (IDUs) (Suriakusumah 2011). It is estimated that these will increase even further, up to 2.8 % drug users (about five million people) in 2015 (Suriakusumah 2011). Besides the direct substance use-related health concerns, drug use is a major factor in the ongoing HIV epidemic in Indonesia. Injecting drug use increased dramatically in the late 90's in Indonesia, acting as the main force driving the HIV-epidemic. Among the general population, the prevalence of HIV-infection is still low (0.3 %), but up to 50 % or more of IDUs are already HIV-infected (Source: National Aids Commission: Country Report on The Follow Up to The Declaration of Commitment on HIV/AIDS: UNGASS Reporting Period 2006–2007. Committee NA 2007). In 2012, from 21,511 patients with HIV infections, 2,461 (>10 %) cases were IDUs (Laporan situasi perkembangan HIV&AIDS di Indonesia tahun 2013). The Integrated Biological Behavioural Surveillance (IBBS 2011) found syphilis infections among IDUs in Indonesia in about 3 % of cases (Integrated Biological and Behavioural Survey 2011). Moreover, substance use is also involved in other forms of transmission risk behavior, including sexual risk behavior (Iskandar et al. 2009).

Since over a decade Indonesia has implemented evidence-based and effective interventions for the prevention and treatment of both substance dependence and HIV/acquired immunodeficiency syndrome (AIDS). Examples are the development of needle and syringe exchange programs (NSPs) and opioid substitution therapy (OST). Besides residential treatment for substance dependence, Indonesia currently has 242 nonresidential facilities that give services for drug users. However, the utilization rate is very poor (only 0.5 %) (Suriakusumah 2011). In addition,

coverage of HIV prevention and treatment strategies for IDUs in Indonesia is similarly low: about 30 % of the Indonesian IDUs make use of an NSP and 1 % of the IDUs are covered by OST programs; importantly only 6 % of the HIV + IDUs received antiretroviral treatment (ART) (Mathers et al. 2010; Mboi 2010).

Several factors contribute to these poor coverage rates, including limited capacity of well-trained professionals; limited consultation time with medical doctors and poor competencies of healthcare professionals in the addiction treatment field, concerning addiction medicine; and limited availability of integrated services for the patient's medical and psychosocial health and stigma to addicted patients both in the society and in treatment centers (Irwanto et al. 2010; Utami 2001; Pinxten et al. 2011). In Indonesia addiction has been criminalized for a long time and has not been regarded as a medical problem. Moreover, addiction medicine is not recognized as a medical (sub)specialty. Indonesia has about 200 professionals working in addiction care, of which about 17 % never ever received training on addiction (Sarasvita 2010). Most of these addiction care professionals only received a short training in OST and/or NSP management (Sarasvita 2010).

Fortunately, in 2009, the law on narcotics was changed. The old law viewed drug users as criminals that had to be punished. The new narcotics act ("Undang-Undang Republik Indonesia Nomor 35 Tahun 2009 tentang Narkotika 2009") states that people with addiction problems should get medical treatment and rehabilitation (Undang-undang Republik Indonesia Nomor 35 tahun 2009 tentang Narkotika 2009). This paradigm change requires specific addiction training of healthcare professionals, for providing evidence-based and effective treatment for these patients.

To date, medical education in Indonesia sometimes only provides addiction medicine training as a one-hour lecture as one of the psychiatric topics for medical students at the preclinical level. There is no formal training in addiction medicine for graduated medical doctors (Utami 2001; Pinxten et al. 2011; Joewana 2012). Only one medical school in Indonesia (Atma Jaya Catholic University of Indonesia, Jakarta) has a curriculum on addiction medicine as an elective, 5-week block that has been established in 2009 (Joewana 2009, 2012).

144.2 Training Features in Addiction Medicine

144.2.1 Current Training on Addiction Medicine in Indonesia

The Ministry of Education in Indonesia developed the Core Curriculum in Medical Education as a guideline for national faculties of medicine in Indonesia (Joewana 2012). In the Core Curriculum 1980, addiction medicine is embedded in 5-hour psychiatric lectures (Joewana 2012). In 1990, the same concept was applied. The new medical curriculum in 2006 ordered medical education to be more competency based and student centered with an excellence competency to be developed by each university (Joewana 2012). One medical faculty chose addiction medicine as one of its excellences and developed addiction medicine training as an elective training block. In addition, the Ministry of Health, National Narcotics

Board, and National AIDS Commission conduct informal short addiction medicine trainings (2–3 days workshop) for medical doctors who work in their healthcare services. There are also specific short training courses such as harm reduction training and training on methadone or buprenorphine maintenance treatment.

144.2.2 The Addiction Medicine Training Need Assessment

As a part of 5-year European Commission-funded, IMPACT program (Integrated Management of Prevention and Control and Treatment of HIV/AIDS), the Bandung Addiction Working Group was developed. Padjadjaran State University (UNPAD) in Bandung, West Java, Indonesia, and the Dutch Maastricht University, Radboud University Nijmegen, the Nijmegen Institute for Scientific Practitioners in Addiction (NISPA), and Antwerp University of Belgium collaborated in order to take the first steps in the development of a national addiction medicine training program (Pinxten et al. 2011; Alisjahbana et al. 2009). This program offered the opportunity to address also the problem of lacking well-trained professionals in addiction medicine.

Early 2010, in the last program year of the IMPACT program, the Bandung Addiction Working Group, consisting of professionals working with IDUs and HIV patient in IMPACT, University of Padjadjaran, and the psychiatric department of Dr. Hasan Sadikin Hospital, supported by the secretary of the National AIDS Commission (Dr. Nafsiah Mboi) and by the senior IMPACT advisor Prof Dr. C. de Jong, director of the Nijmegen Institute for Scientist Practitioners in Addiction (NISPA), joined forces and took the lead in the development of an Indonesian evidence- and competency-based addiction medicine course (Pinxten et al. 2011). On April 1, 2010, the Bandung Addiction Working Group took the initiative to organize an expert meeting of selected Indonesian experts in the field of addiction medicine. During this meeting, these experts searched for professional consensus on the development of a national curriculum for addiction medicine. This first consensus meeting was joined by 13 high-ranking representatives from national addiction treatment centers, professional organizations, and academic training professionals. During this consensus meeting, all participants decided to continue as the Indonesian Addiction Medicine Study Group and to support the development of a national short course on evidence- and competency-based addiction medicine (Pinxten et al. 2011).

During this meeting training needs were assessed using the training needs assessment (TNA) questionnaire. A detailed report is published elsewhere. This questionnaire was based on the medical competencies as defined by the Indonesian Medical Association as well as on international competencies for the Addiction Medicine Specialist derived from the models of the Royal College of Physicians and Surgeons of Canada (Frank et al. 1996), the CanMEDS 2005 Physician Competency Framework "Better standards. Better physicians. Better care" (Frank 2005), the Profile of the Dutch Addiction Medicine Specialist (VVGN 2008), the Dutch Profile Psychiatrist (NVVP 2005) and international programs for Addiction Psychiatry (http://www.acgme.org/acWebsite/home/home.asp), criteria for international certification in addiction medicine (http://www.isamweb.org), and the

SAMHSA (Center for Substance Abuse Treatment 2006). Implications for the medical education in psychiatry were also taken into account (Scheiber et al. 2003).

During the meeting the experts selected the core competencies that should be covered in such a national addiction medicine training curriculum from this extensive list of competencies. This resulted in 30 selected competencies covering three domains:

1. Assessment of substance use disorders
2. Treatment initiation
3. Continued treatment of patients with chronic substance use disorders (Pinxten et al. 2011)

This consensus meeting was followed by a 2-day addiction curriculum workshop for about 35 Indonesian addiction medicine professionals from all over Indonesia. During this workshop the 30 selected addiction medicine competencies were prioritized using a 5-point Likert scale covering all topics previously identified (Pinxten et al. 2011). The participants were also asked to select the ten most important competencies from the list. Based on these ratings, the following ten core competencies for the national addiction medicine curriculum were identified (Pinxten et al. 2011):

- Selecting appropriate screening/assessment tools for substance use disorders
- Screening risk of substance use problems
- Assessing substance use problems by taking a patient's history
- Interpreting substance use by screening, assessment, and lab results
- Formulating a substance use disorder (SUD) diagnosis according to DSM-IV
- Explaining diagnosis, prevention, and treatment plan to the patient
- Developing a written treatment plan
- Selecting indicated initial treatment medications
- Using motivational techniques to support adherence to treatment
- Managing withdrawal

During the second day of the 2-day conference, it was decided that the comprehensive professional training course would include the following seven theoretical modules (Pinxten et al. 2011):

- General introduction including history of addiction and addiction care, co-occurring disorders, and legal aspects
- Basic concepts of addiction including different aspects of the biopsychosocial model
- Psychopharmacological characteristics and neurobiology of psychoactive substances
- Clinical features, assessment, and diagnosis
- Management of treatment
- Addiction care skills, including behavioral and technical competencies
- Monitoring, evaluation, and research

144.2.3 Indonesia Short Course in Addiction Medicine (I-SCAN)

The next step in the development of a national addiction medicine curriculum was to develop the content of this course, based on the professional consensus as

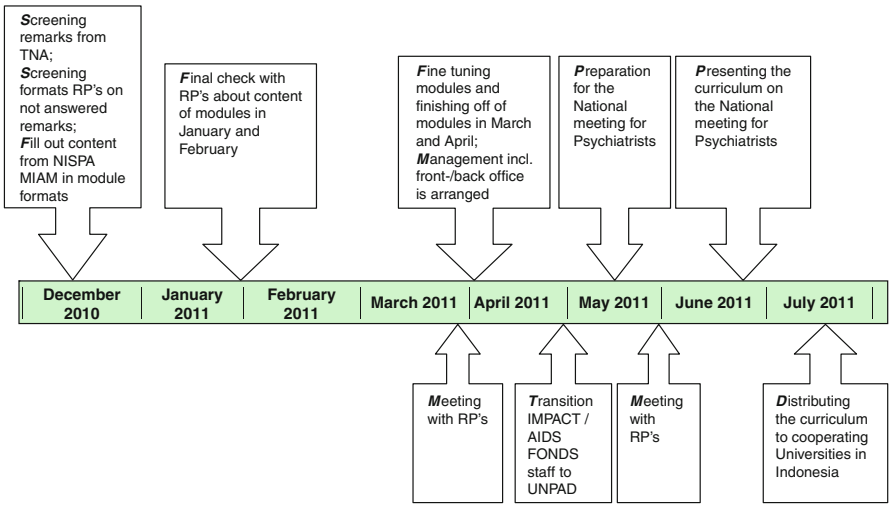

Fig. 144.1 Time line curriculum development Indonesian short course in addiction medicine

described above. Bandung Addiction Group hosted two 2-day workshops for the Indonesian Addiction Study Group. In November and December 2010, a broad alliance of national stakeholders in addiction and HIV care joined forces to further develop a national Indonesian Short Course in Addiction Medicine (I-SCAN). Stakeholders included healthcare professionals, representatives from the Indonesian Psychiatric Association, national and international NGOs, the national AIDS Commission, Ministry of Health, and some universities (University of Indonesia Jakarta, Atma Jaya Catholic University of Indonesia Jakarta, Udayana University Bali, Gadjah Mada University Yogyakarta, and Airlangga University Surabaya).

During this meeting the general objectives were defined, as well as specific objectives per training module. The overall study load of the course was agreed upon (including total contact hours/self-study, practical/field training, research and thesis writing) as well as the mixture of knowledge, attitude, and skills training per training module. Contact persons were identified for each participating organization, resulting in one teaching team per module. In addition a national I-SCAN directorate and secretariat were appointed, as well as a quality control mechanism and certification. Finally, a budget was estimated and a strategy was defined to find additional funding for a first tryout of the I-SCAN.

Following these workshops, the Bandung Addiction Working Group finalized the national curriculum by fine-tuning organizational, logistic, and professional aspects of I-SCAN, including the detailed content, organizing a national Ministry of Health accreditation, and establishing an electronic library of international and national reference publications (Fig. 144.1).

In order to facilitate long-distance learning, the NISPA supported the Bandung Addiction Working Group in the development and installation of an electronic

learning environment (Moodle). By mid-2011 a complete and detailed Indonesian evidence-based addiction curriculum was ready and marketed.

Unfortunately, the kickoff I-SCAN training planned for January 2012 had to be postponed because of several reasons. Targeted participants questioned the practical use of the I-SCAN certification for their carrier: they rather preferred a master type of course that fits in the normal medical career path instead of this 3-month course. Until now, there is no supportive policy from Ministry of Health stating the need for addiction services and addiction medicine training: national policy support is difficult to get at the end of the process; one should start with it. It is difficult to find donor support for a national training: a buy-in process should be started in an early phase of the curriculum development process. Targeted participants were those who already work in addiction services. Without explicit permission from their institution, it is difficult for them to leave their work for joining this 3-month course. Trainers come from several cities in Indonesia; therefore, the fee for joining this course is quite expensive without financial input from national level or from donor side.

144.2.4 Lessons Learned

A successful bottom-up and multi-stakeholder development process by addiction professionals does not guarantee the continuous leadership and momentum needed to mobilize national and international support. We suggest that a major operation like the development of a national curriculum should never start at the end of a donor-funded program. Finally we have to conclude that it is politics that matters at least as much as educational process and professional content.

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ISAM's International Certification of Addiction Medicine: The First Decade

145

Nady el-Guebaly and Claudio Violato

Contents

Abstract

This chapter reviews a decade's effort by the International Society of Addiction Medicine to develop a multiple choice test of knowledge in the field. The process of establishing a pool of questions as well as criteria for eligibility to challenge such an examination is described.

Lessons derived from the repeated administration of the exam are reviewed. An international examination is possible involving questions with good psychometric properties. The challenges of striving for an "a-cultural examination" are reported as well as the necessities of cost accessibility, security, and sensitivity.

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145.1 Introduction

In 1999, the International Society of Addiction Medicine (ISAM) came into being. Its mission was to promote an international agenda, including advancing the knowledge about addiction seen as a treatable disease, advocating for the major role physicians play in its management as well as enhancing the credibility of their role, and, last, developing educational kits accessible to an international audience.

The need for improved medical education in the field is well recognized in both developed and developing countries and is detailed in other chapters of this textbook's section (Crockford and el-Guebaly in press; Ayu and De Jong in press). The call for educating all physicians in playing their respective roles in the care of patients affected with the disorders of addiction has been made repeatedly (Crockford and el-Guebaly in press; Ayu and De Jong in press; Soyka and Gorelick 2009). An increasing number of generalists and specialists physicians are dedicating a major portion, if not all of their practice, to this significant public health issue. Enhancing their credibility and validating their practice through a formal process of certification became a goal of ISAM.

There is a growing international consensus about the core competencies required of every physician in treating abusing or addicted patients. They are *s*creening, *b*rief *i*ntervention including motivational interviewing, and awareness of *r*eferral for *t*reatment options including mutual help. In the USA, these competencies are known by their acronym SBIRT (Madras et al. 2009). By comparison, the boundaries of individual specialty competencies are understandably less defined. Based on core concepts from the basic sciences, evidence-based practices include, but are not limited to, prevention strategies; diagnosis, assessment, and early interventions; detoxification and craving; relapse prevention; psychotherapy, CBT, 12-step, motivational enhancement, contingency management, and cue exposure; psychopharmacology, general and specific including maintenance and medication interaction; physical and psychiatric concurrent disorders, primary or secondary disorders; ethical and legal issues around the workplace, including a physician's own impairment; chronic pain; forensic issues; cultural factors; age and gender issues; and behavioral addictions.

In the USA, the first medical association's certification examination in the field was held in 1983 by the California Society of Addiction Medicine, followed by the first national examination in 1986 under the auspices of the American Society of Addiction Medicine (ASAM). The American Academy of Addiction Psychiatry established the first subspecialty examination under the auspices of the American Boards in 1993, and more recently the American Society of Addiction Medicine has created an independent American Board of Addiction Medicine (ABAM). Currently, those board certifications or diplomas are valid for 10 years. A commitment to maintenance of certification through documented lifelong learning and assessment of practice-based performance is also required. The criteria of eligibility for challenging these examinations limit the access to candidates mostly from within North America.

145.2 The Certification Process

145.2.1 Chronological Development of an International Certification

Based on the US experience, in Sept 2003, in Amsterdam, the Board of the International Society of Addiction Medicine (ISAM) accepted to set up a valid but affordable international certification. An Editorial Board was formed composed of ten senior clinician members of ISAM from seven countries. An expert in medical education research, including examination psychometrics (C.V.), joined that Board.

ISAM recognized three English language multiauthored textbooks, as a repository of current knowledge in the field through their successive editions (Galanter and Kleber 2008; Ries et al. 2009; Ruiz and Strain 2011). These texts are backed by some 150 peer-reviewed journals in the field, ranging from basic science to clinical practice. An increasing number of research institutes are disseminating information across the world, including leading institutions such as, in the USA, the National Institute of Drug Abuse and the National Institute on Alcohol Abuse and Addiction.

To meet the criterion of affordability as well as reducing the differential access to the literature in different parts of the world, the knowledge basis of the examination is from the three identified textbooks with a primary reliance on the *Principles of Addiction Medicine* (Ries et al. 2009). In addition, the nomenclatures of *Diagnostic and Statistical Manual of Mental Disorders*, (4th ed., text rev.; *DSM-IV-TR*; American Psychiatric Association, 2000) and *International Statistical Classification of Diseases and Related Health Problems*, *Tenth Revision* (ICD 10) (http://www.who.int/classsifications/icd/en/; Nedelsky 1954) were also recommended. Soon these nosologies will be updated with a DSM-V and ICD 11 versions.

Next came the draft of multiple choice questions. From the onset, a concerted effort was made to select as many "culture-neutral" questions as possible. Half of the Editorial Board were ASAM certificants and aware of the preponderance of research data based on US populations in the textbooks that would be of lesser significance in other continents. This meant that the epidemiological database had to shift to the data collected by international bodies such as the World Health Organization (WHO) and the United Nations Office of Drug Control. Another implication was the exclusion of questions about national legislation replaced by questions about the International Conventions. At the end, from an initial pool of 450 questions, 200 multiple choice questions (MCQs) were selected at a 2-day meeting in September 2004 in Calgary. It was recommended that four options for each MCQ were sufficient (25 % chance per option instead of five with 20 % chance). From the very onset, it was clearly stated that the certification would be a test of *knowledge* with some clinical *judgment*. The number of questions allocated to each content area was debated at length. It was eventually agreed that the proportion of content questions would reflect the extent of coverage of the topic in the selected textbooks (See Table 145.1).

Table 145.1 List of topics and questions

Content areas	No. of questions[a] (2011)
I. Definitions and core concepts, basic sciences, including neurobiology, epidemiology, and pharmacology	40
II. Diagnosis, assessment, and early intervention, including prevention and family	10
III. Intoxication and withdrawal	12
IV. Treatment, including linkages, pharmacological interventions (opioid), behavior interventions, family, 12-step/spirituality	65
V. Workplace issues/physician health	10
VI. Physical disorders and complications	27
VII. Psychiatric comorbidities and complications	24
VIII. Pain and addiction	12
IX. Children and adolescents	15
X. Behavior addictions	10

[a]Including 25 experimental questions

145.2.2 The Minimum Performance Levels (MPL) Method

To fulfill their mandate of protecting the public, licensure and certification boards in the health professions need to determine which candidates are qualified to attain certification (pass the examinations) or not (fail). Many of these organizations use criterion-referenced testing with predetermined cutoff scores for pass/fail on licensing or certification examinations. There are many ways to set such cutoff scores, but most rely on expert judgment employing empirical approaches such as the Nedelsky (1954) procedure based on the principle of minimum performance levels (MPL). Accordingly, we employed a modified Nedelsky procedure for setting cutoff scores using MPLs.

In this criterion-referenced testing procedure, the total test score MPL is the sum of each item MPL (Violato et al. 2003). The item writer, therefore, sets an MPL for each item. The MPL is the value ranging between 0.25 and 1.0 which reflects the probability that even a *minimally competent* candidate can answer this item correctly. An MPL of 0.25 indicates a very difficult item with an MPL of 1.0 reflecting an easy one.

145.2.2.1 Example Item from an ISAM Examination

An added formulation of buprenorphine designed to discourage intravenous use contains? (**stem**)

(a) Gabapentin (**distracter**)
(b) Nalmefene (**distracter**)
(c) Acetylcysteine (**distracter**)
(*d) Naloxone (**keyed response**)

a = 1.0 b = 0.75 c = 0.75 d = *

$$\text{MPL} = 1/(4 - \text{sum of p}) = 1/(4 - 2.50) = 0.67$$

Each question having undergone a thorough and rigorous editing process receives an MPL. The construction and psychometric analysis of the exam is under the auspices of faculty from the Faculty of Medicine at the University of Calgary.

To renew the pool from September 2006 on, 25 "dummy" or experimental questions were added for psychometric testing and formed the basis of new yearly questions. This is a common practice in the testing industry to identify questions performing well enough to be retained for future test takers.

The current exam is in two parts with an allowed duration of 2:15 h each.

145.2.3 Psychometric Analysis

145.2.3.1 Item Analysis

A complete analysis of the test requires an item analysis. There are three essential features that constitute an item analysis: (1) difficulty of the item, (2) item discrimination, and (3) distracter effectiveness (el-Guebaly and Violato 2011).

The difficulty of the item is the percentage or proportion of people who got the item correct. Item discrimination has to do with the extent to which an item distinguishes or "discriminates" between high test scorers and low test scores. Distracter effectiveness refers to the ability of distracters in attracting responses. A distracter that attracts no response is not effective; it begins to become effective when it attracts some responses.

145.2.3.2 Reliability and Validity

The reliability of scores is assessed using the coefficient α. Coefficient α estimates the amount of variability in applicants' scores that is due to the difference in ability rather than random influences such as guessing. In the initial series of applicants, the reliabilities of all subtests ranged from adequate to good. Validity of a test has to do with extent to which it measures whatever it is supposed to measure. As very careful attention is given to the development of the appropriate sampling of the subject matter and content (i.e., addiction medicine) of the ISAM test, it has adequate content validity. Empirical evidence of validity is sought by evaluating the correlations between the subscales of the test.

145.2.4 Criteria of Eligibility and Applicants' Countries of Practice

To enhance access to the examination by an international audience, the following eligibility criteria were recommended:

- Graduation from a medical school recognized by the WHO
- Valid license to practice medicine from a licensing jurisdiction (national, regional)

- Good standing in medical community, evidenced by at least three letters of recommendation, from *physicians* knowing the applicant for at least 2 years including, if possible, one current ISAM member
- Documented substantial portion of medical practice over a 3-year continuous period in the addiction field
- Peer-supported evidence of continuing education (conferences, workshops, courses, etc.) over the past 3 years

The above criteria seem to be within the reach of all applicants, and no noticeable impediment to access of the required information has been recorded.

FEES: An international money order payable to the *International Society of Addiction Medicine* for $700 US (non-ISAM members), $600 US (ISAM members), and $625 US (Affiliate Societies members) is forwarded, along with the application.

Since 2005, the examination has been held thirteen times. Practitioners from Canada (21 candidates), Egypt (37 candidates), and Saudi Arabia (17 candidates) have formed the bulk of the applicants so far. Candidates from Hong Kong, Iceland, Kuwait, Sudan, Turkey, and Vietnam have also challenged the examination. The overall pass rate has been 75 % so far.

145.2.5 Lessons Learned

In North America, the Canadian Society of Addiction Medicine recognizes both ASAM and ISAM certificates as equivalent. These qualifications are readily recognized to designate experts in courts and with independent medical examinations (IMEs) for a host of insurance and other agencies.

In Egypt, the ISAM certification is recognized by the Ministry of Health as a professional qualifier. The universities have agreed to use the examination as an end of training knowledge qualifier followed by a clinical skills examination.

A dialogue is ongoing, in several countries in Europe, to use the certification as adjunct to local diplomas. Setting a valid and reliable examination is a time- and resource-intensive exercise, and from our experience, the process of testing core knowledge does not need to be duplicated in every country. Potential addition of questions of national interest to the core questions is a possibility.

As the ISAM certification enters its tenth year, a review of the experience leads to the following conclusions:

1. An international certification examination is possible! While the experience so far focuses on Canada and the Middle East, the process is slowly gaining credibility judging from the inquiries from other regions. As of this year, the examination is available to international fellows training in North America's leading institutions. Local leadership support to disseminate information and promote the value of a clinical knowledge qualifier is critical.
2. The questions show good discriminatory performance. Following the first exam set of 200, 9 questions were dropped and new ones added from the pool, and 36 others had their MLP readjusted, "raising the bar." To renew the pool,

25 "dummy" questions are added to be tested in each examination. A major editorial update was conducted in 2010 and 2011, resulting in the replacement of one third of the questions by new ones and another third being modified. Only the references of the remaining third were updated. The third cycle of editorial update will begin next year.

3. The careful development of the ISAM test has resulted in evidence for both validity (content, empirical) and reliability (internal consistency) and items that are carefully reviewed and evaluated for difficulty, discrimination, and distracter effectiveness.
4. The recommended curriculum should inform examination and vice versa. Topics where the candidates are the weakest included pain and addiction; behavioral addictions; and diagnosis, assessment, and early intervention. In several countries, the field of addiction is limited to the management of substance misuse. Addition of "local" questions to the core examination has been proposed to accommodate the local legislative and possible cultural needs.
5. An "a-cultural" examination may be only a goal to strive for. Biological or laboratory tests may be largely culture-free, although epigenetic findings are showing a number of ethnic differences. Epidemiological data, psychological treatments, mutual help resources, and workplace guidelines are more influenced by the local culture. Many countries forbid the use of methadone maintenance, for example. Can a core examination be fair globally when the medical practices are subject to different cultural and economic constraints? Candidates appreciate the need to be aware of evidence-based treatment options available in other parts of the world and may promote their culturally sensitive adaptation in their own country.
6. The cost, integrity, and sensitivity of the examination are critical in all areas of the world but particularly in developing countries.
7. We continue to rely on standard textbooks, which are updated regularly. Increasingly, these texts are available in electronic versions and may be published with a companion set of questions. So far, few of these questions adhere to exam setting standards but may serve as good training exercises. The ISAM textbook where this chapter will appear aims at further collating international practices.
8. Each successful candidate receives a numbered certificate to avoid forgery. Displays of association membership certificates in practitioners' offices as evidence of competence have been reported. This increases the need for a recognized certificate, testing clinical knowledge through MCQs, and clinical vignettes.
9. The repeated experience of the examination in developing countries is that the pool of often university-based candidates readily achieves pass and higher scores. This pool is however finite. This observation calls for enhanced national efforts to increase the pool of justified candidates practicing evidence-based medicine across the nation.

10. Presenting standardized review courses and complementing the test of clinical knowledge with a standardized objective structural clinical exam (OSCE), administered locally, is the next frontier.

There is no doubt that language proficiency can be a barrier. Discussions have been underway to translate the examination into Spanish and Italian. Settings where a computerized version of the examination can be administered are being contemplated. The security of this process may be improving. The cost remains significant. The search for funding support is ongoing. Several examination sets are being administered by different academic institutions worldwide; must we reinvent the wheel time and time again?

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Navigating Access to Addictions Literature: The Hubert H. Humphrey Fellowship Experience

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Nita Bryant

Contents

Abstract

Treatment providers lacking access to university libraries and/or costly journals have greater access than ever before to the scientific literature in the field and to the companion gray literature that distills the science into practical information. Educational sources essential for understanding and engaging in evidence-based practice (EBP) are also increasingly available online free of charge. While this is clearly cause for celebration, awareness of these resources is low, and navigating this highly complex and disjointed literature terrain can be daunting without professional guidance. The intent of this chapter is to raise awareness of these complementary sources, demonstrate their scope and utility, and encourage their use.

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146.1 Introduction

Evidence-based practice requires a wide range of competencies. Among the most important is the ability to translate clinical problems from every day practice into focused questions that facilitate efficient evidence searches. Equally important is the ability to read and critically appraise the primary evidence for rigor, relevance, and utility (Carr et al. 2011; Mokhtar et al. 2012). Busy clinicians may prefer to utilize time-saving pre-appraised information like systematic reviews, evidence-based synopses, and clinical practice guidelines (Ilic 2009). Unfortunately, while evidence for answering many clinical questions exists, it may not be easily accessible (Leffler et al. 2013). For treatment providers lacking access to university libraries and/or costly journals, retrieving this essential literature can be problematic. One means of bridging this gap lies in the growing body of "gray literature" that is available from organizations directly involved in science-based addiction technology transfer efforts (Clark 2002; Condon et al. 2008). Disseminated via governmental websites rather than peer-reviewed journals or commercial publishing routes, gray literature includes bulletins, research reports and summaries, best-practice guidelines, training materials, and technical manuals (Alberani et al. 1990). Although not considered "scholarly" per se, this vital information effectively distills the best available scientific evidence into a language that makes findings accessible to a wide audience of stakeholders (Brown 1995). As such, gray literature is an essential complement to primary research in the field (Marinelli-Casey et al. 2002; Coomber et al. 2003; McGrath et al. 2006; Lin and Vaska 2009; Ali et al. 2010).

Until recently, much of this primary research has been too costly and out of reach (Brower 2010). Through the collective efforts of organizations like the International Network for the Availability of Scientific Publications (INASP), journal publishers, research institutions, scientific societies, librarians, and research funding agencies, these economic barriers are being dismantled in favor of open access (OA) publishing models and public access policies that make research available online free of charge to anyone with an Internet connection. The rapid and efficient global dissemination of research findings also increases the visibility of research from emerging countries (Arunachalam 2003), allowing everyone to build on the science, experiences, and culturally specific approaches of other nations. Taking full advantage of this openness, however, requires a solid foundation in evidence-based skills.

While EBP is being integrated into graduate and training programs worldwide, many professionals have not been sufficiently trained in EBP techniques (Leffler et al. 2013; Mokhtar et al. 2012). Fortunately, introductions to and continuing education EBP modules are widely available on the web. These sources complement the gray literature and open access publications which have made essential information more widely available to the field than ever before. While this is clearly cause for celebration, awareness of these resources is low, and navigating this highly complex and disjointed literature terrain can be daunting without professional guidance (Lin and Vaska 2009; Brower 2010). The intent of this chapter is to raise awareness of these valuable information sources and guide readers to sources that might otherwise go untapped.

146.2 Open Access Features

146.2.1 Setting and Methods

The chapter draws insight from the experiences of Hubert H. Humphrey Fellows affiliated with the Institute for Drug and Alcohol Studies at Virginia Commonwealth University in the USA (www.vcu.edu/idas/humphrey.html). The Humphrey program, which is funded jointly by the US State Department and the National Institute on Drug Abuse, brings mid-career professionals from developing nations to the USA to learn about evidence-based government policy, prevention, and treatment programs. Representing a wide spectrum of stakeholders, fellows include attorneys, clinical psychologists, correction officers, educators, forensic toxicologists, government and NGO consultants, physicians, and social workers from Brazil, Kazakhstan, Myanmar, Nigeria, Sri Lanka, Togo, Trinidad and Tobago, Uganda, and Uruguay. Despite their professional and geographic diversity, Fellows share common needs and concerns: locating evidence-based sources they can adapt to specific regional contexts, maintaining access to resources after leaving the university and losing library privileges, and feeling lost in the maze and sheer volume of available information.

These needs and concerns generated a lengthy search for solutions and led to the development of a Drugs and Alcohol Research Guide (http://guides.library.vcu.edu/drugs-alcohol). The portal facilitates access to OA publications and gray literature, reduces the volume of resources to a select few, and can be accessed by anyone with an Internet connection. It also includes educational sources for continuing education in EBP. The development of the portal required an extensive review of websites and electronic databases that might include open access resources. These were then narrowed down by assessing their scholarly merit, utility, relevance, and stability. It also required an extensive search for gray literature produced by credible noncommercial organizations directly serving the practical needs of stakeholders in the field. This vetting process required a substantial investment of time and effort, but the selected resources free users from sorting through the larger volume and variable quality of online information regarding addiction. This chapter draws selected examples from the portal to demonstrate the nature, scope, and utility of these sources; provides information about how to locate addictions research, gray literature, and evidence-based practice sources; and includes an annotated list of useful websites and search tools.

146.2.2 Open Access to Scholarly Research

The prevention and treatment of addictions depend on access to and sharing of primary research worldwide. Today, this is becoming increasingly possible through the growth of OA articles that appear in traditional journals; through peer-reviewed fully OA journals in medical, social, and behavioral sciences that include research in addictions; and through a small subset of subject-specific journals. The latter

include *Addiction and Health* (published by the Kerman University of Medical Sciences and Health Services, Iran), *Addiction Science & Clinical Practice* (previously published by NIDA), *Harm Reduction Journal* (affiliated with Harm Reduction International and the Eurasian Harm Reduction Association), *Heroin Addiction and Related Clinical Problems* (official journal of EUROPAD), *Substance Abuse*: *Research and Treatment* (published in partnership with HINARI, the World Health Organization's Access to Research in Health Programme), and *Tobacco Induced Diseases* (the official journal of the International Society for the Prevention of Tobacco Induced Diseases).

146.2.3 OA Journal Repositories

Most OA journal publishers deposit articles in searchable, internationally recognized OA repositories like PubMed Central (PMC) in the USA (www.ncbi.nlm.nih.gov/pmc/), PMC Canada (http://pubmedcentralcanada.ca/pmcc/), and Europe PMC (http://europepmc.org/). These are repositories for author manuscripts submitted in compliance with public access policies mandated by funding agencies. Among these bodies are the US National Institutes of Health (NIH), the Canadian Institutes of Health Research (CIHR), the National Research Council's Canada Institute for Scientific and Technical Information (NRC-CISTI), the European Research Council, and the Wellcome Trust.

146.2.4 Institutional Repositories

The momentum of the OA movement is evident in the growth of institutional repositories that collect, preserve, and freely disseminate the intellectual output of colleges, universities, research organizations, and institutions. The Directory of Open Access Repositories/OpenDOAR (http://www.opendoar.org/search.php) enables users to search across all available repositories from Africa, Asia, Australasia, the Caribbean, Central America, Europe, North America, Oceania, and South America simultaneously using a familiar Google Custom Search Engine (CSE). Because PubMed Central is among these depositories, OpenDOAR can be a valuable starting point and discovery tool for locating journal articles, relevant theses, dissertations, research reports, and working papers from international organizations that would otherwise be hard to locate.

While OA is not yet the default method for distributing new peer-reviewed research in the biomedical sciences, it is gaining momentum globally and represents an essential chain of communication from researcher to practitioner (Chan et al. 2009). As such, awareness of these resources and how to access them is important for researchers and practitioners alike (Brower 2010). Equally important is the ability to critically appraise the quality and rigor of research articles, an essential component of EBP. Many for-profit OA publishers claiming to be legitimate are not. Jeffrey Beall, a librarian at the University of Colorado, in Denver

(USA), maintains a continuously updated list of suspect ("predatory") publishers available at http://scholarlyoa.com/publishers/. In this environment, the need for critical appraisal skills is clear.

146.2.5 The Role of Gray Literature in Addiction Treatment: *Translating* Research to Practice

The term "translate" aptly describes the problem at hand. Research scientists and practicing professionals have very different missions, roles, means of communication, and information needs (Leckie et al. 1996; Marinelli-Casey et al. 2002; Ali et al. 2010; Rosa et al. 2012). A professional's time is devoted to task-oriented activities that arise from serving multiple roles simultaneously. For instance, Humphrey Fellows may need to develop a prevention or treatment program that is compatible with conditions in their home countries, demonstrate the need for doing so to policy makers and funders, and then educate and recruit community leaders and counselors to help carry it out. Although these interrelated activities must be informed by the best available scientific evidence, much of the practical information will not be found in peer-reviewed journal articles. Fellows often require information delivered in specific formats like implementation manuals or in PowerPoint slides explaining the components of an intervention program. They require information delivered in nontechnical language that makes it accessible to a wide audience of constituents and influencers (Brown 1996).

Over the last several decades, local, national, and international agencies have emerged to meet these practice needs, and today, this type of information is widely available. Agencies like the National Institute on Drug Abuse (NIDA) in the USA, the European Monitoring Centre for Drugs and Drug Addiction (EMCDAA), and the World Health Organization's Department for the Management of Substance Abuse disseminate tools for planning, screening, training, assessment, continuing education, and other needs that arise in the course of day-to-day practice. Considering the importance of gray literature to the addictions field, knowing how to access it is essential (Lin and Vaska 2009). Given the sheer volume of this literature, however, navigating it can be a daunting task. There are simply far too many relevant websites to search them all regularly, and many of these sites can be overwhelming in and of themselves. One solution to this problem is a single portal enabling users to search across multiple potentially relevant sites simultaneously (LaPelle et al. 2006). The Google Custom Search Engine described below does just that.

146.2.6 Intergovernmental Organization (IGO) Search Engine

Global in scope, the Intergovernmental Organization (IGO) Search Engine (http://www.google.com/cse/home?cx=006748068166572874491%3A55ez0c3j3ey) was

launched by David Oldenkamp, International Documents Librarian at Indiana University. It has proven a valuable tool for locating a wide range of technical manuals, reports, and other materials relevant to the needs of international addiction practitioners. An example of a search carried out at the time of this writing demonstrates the reach, relevance, and utility of this Google Custom Search Engine. Searching "*evidence-based*" *implementation* "*needle exchange program*" generated results that included a World Bank policies and procedures manual for starting and managing needle and syringe programs, a literature review of international prison-based syringe exchange programs carried out by NDARC (the National Drug and Alcohol Research Centre at the University of New South Wales), a legal framework for needle exchange programs from the European Monitoring Centre for Drugs and Drug Addiction, and a guide to evaluating needle exchange programs from Harm Reduction International.

146.2.7 Selected Resources

This section provides an annotated list of evidence-based resources chosen for their relevance to the needs of Humphrey Fellows. The sample sites provide tools that focus on workforce and organizational development for effective program implementation; tools for planning, monitoring, and evaluating program activities; instruments for assessing the extent of drug use in their home countries; and opportunities for continuing professional education. As such, the selected sources should be of value to an international audience of addiction professionals.

146.2.7.1 Addiction Technology Transfer Centers (ATTCs)

In the USA, the National Institute on Drug Abuse (NIDA) and the Substance Abuse and Mental Health Services Administration (SAMHSA) are charged with the task of moving of important scientific findings into mainstream addiction treatment practice. SAMHSA's Addiction Technology Transfer Center (ATTC) Network is one of the primary vehicles for accomplishing this task (http://www.attcnetwork.org/explore/priorityareas/). Focused on workforce development, the ATTC Network is committed to improving the competency of current and future practitioners primarily by creating and expanding continuing education courses and modules. Of particular note is *The Change Book*: *A Blueprint for Technology Transfer*. It includes evidence-based principles, steps, strategies, and activities for implementing change initiatives that improve prevention and treatment outcomes across multiple interacting systems. At the time of this writing, *The Change Book* had been downloaded more than 21,000 times from the ATTC Network website above. Through the ATTC Online Learning Portal (http://www.attcelearn.org/), frontline counselors, clinical supervisors, administrators, and students can enroll in free online self-paced courses that range from essential substance abuse skills, foundations for working with addictions, to clinical supervision foundations to foundations of SBIRT.

146.2.7.2 SAMHSA's Knowledge Application Program (KAP) (http://kap.samhsa.gov/index.htm)

SAMHSA's KAP resources include the TIPS (Treatment Improvement Protocols) Series. Each TIP contains best-practice guidelines for topics that range from *Improving Treatment for Drug-Exposed Infants* (TIP 5) to *Comprehensive Case Management for Substance Abuse Treatment* (TIP 27). The TAPS (Technical Assistance Publications) Series provides practical guidance and information related to the delivery of treatment services. Among these are *Addiction Counseling Competencies*: *The Knowledge*, *Skills*, *and Attitudes of Professional Practice* (TAP 21) and Competencies *for Substance Abuse Treatment Clinical Supervisors* (TAP 21A). KAP Curriculum packages include trainers' manuals, participants' manuals or handouts, and PowerPoint/overhead slides. For instance, the *Therapeutic Community Curriculum Trainers Manual* provides teaching materials for an 11-module training course designed to help new employees in a therapeutic community (TC) understand fundamental TC concepts. Included are step-by-step presentations, reproducible resource sheets, and PowerPoint slides. Many KAP materials are adapted for consumers or clients whose first language is not English.

146.2.7.3 Methadone Research Web Guide and Tutorial (http://international.drugabuse.gov/educational-opportunities/certificate-programs/methadone-research-web-guide)

Part of the NIDA International E-Learning Certificate Program Series, this Web Guide gives a basic overview of research supporting approval of methadone maintenance as a viable opioid treatment therapy in the USA. It answers the most frequently posed questions by the international community regarding the path of research inquiry used by the USA to support approval of methadone as a treatment therapy. The tutorial addresses questions in four subject areas, and each question links to the Methadone Research Web Guide for more information. Readers may answer the questions before or after reviewing the full Web Guide or concentrate on the section of the Web Guide that is most relevant to them.

146.2.7.4 Motivational Incentives Suite: A NIDA-SAMHSA Blending Initiative (http://www.bettertxoutcomes.org/motivationalincentives/index.html)

This collection of tools assists organizations along a continuum from raising awareness about motivational incentives (also referred to as contingency management) through dissemination and implementation activities. PAMI (Promoting Awareness of Motivational Incentives), an introductory training tool, exposes organizations to the principles of MI and demonstrates evidence of clinical effectiveness. Behavioral health-care practitioners can then deepen their knowledge through participating in the free, self-guided, interactive online course, Motivational Incentives: Positive Reinforcers to Enhance Successful Treatment Outcomes (MI: PRESTO). Of particular note, treatment organizations can also access additional implementation support through the Motivational Incentives Implementation Software (MIIS), developed by the National Institute on Drug Abuse and available

at no cost. This desktop software provides mechanisms for maintaining patient information and Motivational Incentive activities.

146.2.7.5 Global Assessment Programme on Drug Abuse/GAP (http://www.unodc.org/unodc/en/GAP/index.html)

The United Nations Office on Drugs and Crime (UNODC) distributes the GAP methodological toolkit to strengthen the global information base on drug abuse through the use of harmonized indicators among Member States. The toolkit includes eight modules covering topics that include indirect methods for estimating prevalence, measurement of drug treatment demand, conducting school surveys on drug abuse, and data management. Most of the modules are available in English, French, Russian, Spanish, and Arabic.

146.2.7.6 Treatnet Training Package (http://www.unodc.org/treatment/en/training-package.html)

This is the largest international training initiative in the addictions. Treatnet, a 20-country UNODC international consortium, is currently active in drug dependence treatment service improvement projects in Africa, Central Asia, the Middle East, South America, and Southeast Asia. . . The curriculum emphasizes evidence-based addiction treatment practices with a strong empirical foundation. The four-volume training package created for this initiative covers Screening, Assessment and Treatment Planning; Elements of Psychosocial Treatment; Addiction Medications and Special Populations; and an Administrative Toolkit. It also includes a question-by-question manual for using the Addiction Severity Index (ASI), an addiction assessment tool widely used throughout the USA and in other countries.

146.2.7.7 Best-Practice Portal (http://www.emcdda.europa.eu/best-practice)

Developed by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), this portal is focused on illicit drugs and polydrug use in Europe. The portal is structured by thematic modules that include the available evidence for prevention (families, schools, communities), treatment (amphetamines, cannabis, cocaine, opioids), harm reduction (opioid injectors, stimulant injectors, non-injecting drug users), and social reintegration (drug treatment, criminal justice, housing, education/vocational training, employment). Of particular note is the Evaluation Instruments Bank (http://www.emcdda.europa.eu/eib), an extensive online archive of freely available instruments for treatment, prevention, or harm reduction interventions.

146.2.7.8 SAMHSA's National Registry of Evidence-Based Programs and Practices (NREPP) (http://www.nrepp.samhsa.gov/)

NREPP is a searchable online registry of more than 260 interventions supporting mental health promotion, substance abuse prevention, and mental health and substance abuse treatment. Each intervention is independently reviewed to rate

the strength of available implementation materials, training and support resources, and quality assurance procedures. Each intervention includes cost information and provides contact information. The latter enables potential adopters to talk to intervention developers directly and learn how to implement these approaches in their own communities.

146.2.7.9 Tools and Education for Clinical Decision Making

Locating evidence to inform decision making requires an understanding of evidence levels; the ability to formulate a clinical question based on the PICO model (identifying patient/ intervention/ comparison/outcome); knowing how and where to search for primary sources; and understanding where, how, and why to look for secondary sources. The latter includes systematic reviews, evidence-based synopses, and clinical practice guidelines which save busy clinicians valuable time (Ilic 2009). They represent the accumulated evidence on common clinical interventions that are essential for clinical decision making, and yet use of these resources is relatively low (Andrews et al. 2005; Lasserre et al. 2011; Thomson 2013). One problem is that they are spread out among so many websites that choosing which one to use and/or navigating dissimilar interfaces can be a daunting task (LaPelle et al. 2006). Equally problematic, many clinicians lack the requisite knowledge and search skills to take advantage of them (Schardt et al. 2007; Cullen et al. 2011; Judd and Kennedy 2011). The final resources on this list help mitigate these problems.

146.2.7.10 The Centre for Evidence-Based Medicine (CEBM)

The CEBM at the University of Oxford provides a suite of online tools enabling health-care professionals to maintain the highest practice standards. The suite includes tutorials on asking well-built clinical questions, the systematic retrieval of the best evidence available, critical appraisal of evidence for validity, clinical relevance and applicability, the application of results in practice, audit and feedback of clinical practice to improve performance, and designing trials or assessing research design. It also provides a computer-assisted critical appraisal software tool (CATmaker) that can be downloaded free of charge. This enables users to create critically appraised topics (CATs) for the key articles they encounter about therapy, diagnosis, prognosis, etiology/harm, and systematic reviews of therapy. All can be accessed via http://www.cebm.net.

146.2.7.11 Evidence Based Behavioral Practice (EBBP)

Funded by the US Office of Behavioral and Social Sciences Research, National Institutes of Health, this site provides online training enabling users to conduct the steps of the EBBP process with a simulated client and/or community, learn about the shared decision-making process as a practitioner working through cases and client preferences in a clinical setting, and use two real-world case examples to understand and practice implementing evidence-based practices. These and more modules are accessible via http://www.ebbp.org/training.html with free registration.

146.2.7.12 TRIP Database (Turning Research into Practice) (http://www.tripdatabase.com/)

TRIP is a free meta-search engine enabling users to search 150 health resources simultaneously, including MEDLINE, Bandolier, BestBets, POEMs, Clinical Evidence, and the Cochrane Library, which is internationally recognized as the highest standard in evidence-based health care. Using a simple interface, users can access best evidence categories that include evidence-based synopses, clinical questions, systematic reviews, and guidelines (North America, Europe, others) and more. To facilitate effective searching, the database provides a "PICO" search feature prompting users to create a structured clinical question targeting a specific population, intervention, comparator (if relevant), and outcomes (Meats et al. 2007). This increases the likelihood of efficiently locating high-quality, current evidence directly relevant to practice needs (DiCenso et al. 2009). For instance, a recent search for "injecting drug users," "needle or syringe exchange," and "cost-effectiveness" generated 11 sources including systematic reviews and clinical guidelines from Australia/NZ, Canada, the UK, and the USA. For users who need additional help understanding this approach, the TRIP database conveniently links to tutorials from the Centre for Evidence-Based Medicine mentioned above (http://www.cebm.net/?o=1036). Considering that well-built clinical questions are the key to evidence-based decision making and that access to systematic reviews, evidence-based synopses, and clinical practice guidelines save clinicians time, TRIP is a valuable tool on multiple counts.

146.3 Conclusion

As a result of the open access movement in scholarly communications, addiction professionals have greater access than ever before to the scientific literature in the field. Access to the companion gray literature that distills and translates this science into practical information is also widely available. The growth of these complementary resources has coincided with the fortuitous rise of free EBP tutorials for clinicians and other health-care providers in the field. The intent of this chapter was to raise awareness of these sources, demonstrate their scope and utility, and encourage their use. Readers are also encouraged to visit the Drugs and Alcohol Research Guide available via http://guides.library.vcu.edu/drugs-alcohol. Hopefully, users will benefit from the sources reviewed here as have the Humphrey Fellows whose concerns shaped this endeavor.

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NIDA International Fellowships: Research Training for Addiction Specialists

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Steven W. Gust

Contents

Abstract

The demand for drug treatment remains largely unmet. According to the World Health Organization, only 1 in 5 people who need drug treatment receives it, and there are only 1.7 treatment beds per 100,000 people. The American Academy of Psychiatrists in Alcoholism and Addictions and the Association for Medical Education and Research in Substance Abuse *Consensus Standards for Postgraduate Medical Fellowships in Alcoholism and Drug Abuse* call for training opportunities that help physicians learn to design, conduct, and interpret drug abuse research studies and introduce addiction specialists to the principal drug abuse research organizations. The National Institute on Drug Abuse (NIDA) International Program fellowships are reviewed, including details about the research training and professional development opportunities provided and the career levels and citizenship requirements for applicants. The professional advantages of NIDA International Program fellowships include a global network of drug abuse scientists working collaboratively to develop, validate, and implement evidence-based treatment and prevention programs around the world.

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147.1 Introduction

Building a global cadre of addiction specialists is a crucial task: Illicit drug use is one of the top 20 risk factors to health (United Nations Office on Drugs and Crime [UNODC] 2009). The *World Drug Report 2012* reports that drug abuse costs lives, contributes to disease, and reduces productivity. Globally, 1 in 100 adult deaths is due to illicit drug use. Injecting drug use – a primary vector for transmission of HIV and other infections – is reported by 148 countries, and 120 of those countries report HIV among the injecting drug-user population. In 2010, 20 % of injection drug users (IDUs) had HIV, 46.7 % had hepatitis C, and 14.6 % had hepatitis B. Drug abuse costs society in terms of lost productivity, which UNODC estimates to be nearly 1 % of the US gross domestic product (GDP), and in drug-related crime, which in England and Wales amounted to 1.6 % of GDP (UNODC 2012). The Joint UNODC/WHO Programme on Drug Dependence Treatment and Care found that the economic cost of drug abuse approaches 2 % of GDP in some countries (UNODC 2009).

The demand for drug treatment remains largely unmet: Only 1 in 5 people who need drug treatment receives it, and there are only 1.7 treatment beds per 100,000 people (World Health Organization [WHO] 2012). In 2008, only 30 % of countries offered pharmacotherapy with treatment medications that have been proven effective (WHO 2012).

In the United States, 23 experts in academic medical training for the addiction field developed *Consensus Standards for Postgraduate Medical Fellowships in Alcoholism and Drug Abuse* for the American Academy of Psychiatrists in Alcoholism and Addictions and the Association for Medical Education and Research in Substance Abuse. These national consensus standards called for "a meaningful, supervised research experience" to help physicians learn to design, conduct, and interpret research studies in drug abuse epidemiology, genetics, pharmacology, social theories, psychology, toxicology, and treatment outcomes (Galanter et al. 1991, p. 6). The standards also recommended that addiction specialists be introduced to the principal drug abuse research organizations. The need for addiction specialists is especially acute in developing countries (WHO 2010). Medical students who participate in mentored research programs develop positive opinions about both clinical care and academic research in substance abuse (Solomon et al. 2003; Truncali et al. 2012).

147.2 Fellowships To Advance Careers in Addiction Research

147.2.1 Fellowships Supported by the NIDA International Program

For more than two decades, National Institute on Drug Abuse (NIDA) International Program fellowships have trained drug abuse research experts from other countries

in US research methods, helped fellows enhance their understanding of the scientific basis of drug abuse and addiction, and introduced NIDA grantees to talented drug abuse researchers from other countries. Fellows join a network of drug abuse scientists working to develop, validate, and implement evidence-based treatment and prevention programs around the world.

NIDA International Program fellows have studied every aspect of addiction, beginning with the underlying biomedical and behavioral causes and progressing through drug use patterns and trends; prevention and treatment interventions; individual, familial, and societal consequences; and policy studies that compare and contrast the effect of government actions across borders. Current scientific questions in global addiction research include treatment of stimulant abuse; demonstrating accessible, acceptable, and affordable models of drug treatment; testing new formulations of effective medications; hepatitis C virus treatment strategies for drug users; effective models to integrate risk reduction interventions with addiction treatment protocols; and diversion and abuse of prescribed medications.

In addition to research training in their specific area of expertise, NIDA International fellows participate in professional development programs throughout the year. While they are in the United States, fellows attend scientific meetings, meet with officials from NIDA and the John E. Fogarty International Center at the National Institutes of Health (NIH), learn about online resources supported by the International Program and the National Library of Medicine, and network with one another. Scientific conferences and social media help fellows stay connected after they return home.

NIDA International Program fellowships provide research training and professional development opportunities for scientists at every stage of their careers, from postdoctoral students to senior researchers. Junior researchers may receive 12 or 18 months of postdoctoral training through the INVEST, INVEST/Clinical Trials Network (CTN), US–Mexico Drug Abuse Prevention, and International AIDS Society (IAS)–NIDA Drug Use and HIV/AIDS Research Fellowships. The NIDA Hubert H. Humphrey Drug Abuse Research Fellowships for midcareer drug abuse professionals enhance the 10 months of mentored academic study offered by US Department of State Hubert H. Humphrey Fellowships by providing additional mentoring and professional development activities. Senior scientists may receive support for short-term research exchanges through the Distinguished International Scientist Collaboration Awards (DISCA) and the Distinguished International Scientist Collaboration Awards for US Citizens (USDISCA). Individuals interested in the NIDA Hubert H. Humphrey Fellowships use the US Department of State application process. All other applicants identify a potential mentor and develop a fellowship proposal in conjunction with that mentor. Table 147.1 provides details about the career level, audience, features, and application deadlines for each fellowship. Additional details are available on the NIDA International Program

Table 147.1 NIDA International Program fellowships

Career level	Program name	Eligible audience	What fellowship includes	Application deadline
Postdoctoral training	INVEST Drug Abuse Research Fellowship	Non-US citizens with a doctoral degree in medicine, public health, or biomedical, behavioral, or social sciences with a minimum of 2 years of postdoctoral research experience	Provides 12 months of postdoctoral training with an established NIDA-supported drug abuse and addiction scientist at a US institution. Each fellow receives training in drug abuse research methods while developing and conducting research under the guidance of a mentor	April 1
	INVEST/Clinical Trials Network (CTN) Drug Abuse Research Fellowship	Non-US citizens with a doctoral degree in medicine, public health, or biomedical, behavioral, or social sciences with a minimum of 2 years of postdoctoral research experience	Provides 12 months of postdoctoral training in the United States with a NIDA-supported drug abuse and addiction scientist affiliated with 1 of the 13 NIDA CTN Regional Research and Training Centers. Each fellow receives training in drug abuse research methods while developing and conducting research under the guidance of a mentor	April 1

	US–Mexico Drug Abuse Prevention Research Fellowship	Mexican citizens or permanent residents with a doctoral degree in medicine, public health, or biomedical, behavioral, or social sciences with a minimum of 2 years of postdoctoral research experience	Provides 12 months of postdoctoral drug abuse prevention research training with an established NIDA-supported scientist at a US institution. Each fellow receives training in drug abuse prevention research methods while developing and conducting research under the guidance of a mentor	April 1
	International AIDS Society (IAS)–NIDA Research Fellowship in Drug Use and HIV/AIDS	Junior scientist with doctoral degree (e.g., Ph.D., M.D.)	Provides an 18-month postdoctoral training fellowship, focusing on HIV and drug use, at a leading research institute with a mentor who is an expert in HIV-related drug use research	Check NIDA website for details: www.drugabuse.gov/international/fellowships-landing
Midcareer training	NIDA Hubert H. Humphrey Drug Abuse Research	Drug abuse professionals from eligible low- and middle-income countries	Provides a 10-month, midcareer, nondegree fellowship to study and work with professionals in the United States. Fellows learn about NIDA-supported drug abuse research and the application of research to the development of science-based government policy and prevention and treatment programs	Deadlines vary. Check with the US embassy or Fulbright Commission in your country

(*continued*)

Table 147.1 (continued)

Career level	Program name	Eligible audience	What fellowship includes	Application deadline
Senior researcher opportunities	Distinguished International Scientist Collaboration Award (DISCA)	Non-US citizen senior researcher with a minimum of 7 years of experience in drug abuse research beyond the postdoctoral level	Supports a professional exchange visit between a drug abuse researcher from another country and a NIDA-funded US scientist. The international drug abuse researcher applies to visit his/her US partner, for up to 3 months, to complete a project best conducted in the United States	January 1
	Distinguished International Scientist Collaboration Award for US Citizens and Permanent Residents (USDISCA)	NIDA-funded US researcher with a minimum of 7 years of experience in drug abuse research beyond the postdoctoral level	Supports a professional exchange visit between a NIDA-funded US scientist and a drug abuse researcher from another country. The US scientist applies to visit his/her international partner, for up to 3 months, to complete a project best conducted outside the United States	January 1
	International AIDS Society (IAS)–NIDA Research Fellowship in Drug Use and HIV/AIDS	Senior scientist involved in HIV-related research, with a minimum of 7 years of experience beyond the postdoctoral level and with a documented scientific record	Provides an 8-month professional development fellowship focusing on HIV and drug use at a leading research institute, for a well-established HIV scientist not currently active in the drug abuse field	Check NIDA website for details: www.drugabuse.gov/international/fellowships-landing

For more information, visit ▶ www.drugabuse.gov/international<RefTarget TargetType="URL" Address="http"//www.drugabuse.gov/international/"/>

website, ▶ www.drugabuse.gov/international<RefTarget TargetType="URL" Address="http"//www.drugabuse.gov/international/"/>.

147.2.2 Professional Advantages of a NIDA International Program Fellowship

As of December 2013, there were more than 415 former NIDA International Program fellows representing 104 countries, from Afghanistan to Vietnam. These individuals play uniquely influential roles in the international drug abuse research community by participating in national, regional, and international research groups; publishing articles in peer-reviewed journals; directing university training and research programs; and leading policy initiatives. Former NIDA International Program fellows lead drug abuse research efforts in every part of the world: They direct academic drug abuse research centers in Brazil, China, Georgia, Indonesia, and Israel and coordinate NIH-supported regional research projects in Eurasia, Latin America, Russia and the former Soviet Union, and Southeast Asia. Former NIDA International Program fellows work for international organizations such as WHO, UNODC, Joint United Nations Programme on HIV/AIDS, and Colombo Plan Drug Advisory Programme in Southeast Asia. They hold positions in drug policy and nongovernmental organizations. Two former fellows work for NIDA.

A 2012 assessment conducted by Virginia Commonwealth University (VCU) found that 1 year after completing their fellowships, more than half (63 %) of the Hubert H. Humphrey Fellows who attended VCU from 2007 through 2010 had a new job; 71 % said their fellowship helped them obtain the new job, and 70 % reported that the new job represented a change in career goals. More than one-third (37 %) of the fellows reported having conducted research since completing their fellowship, and 33 % reported continuing collaborations with a US partner (Leonchuk et al. 2012). The 2010 VCU assessment of fellows from 2007 through 2009 found that most former fellows (40 %) managed or administered treatment or prevention programs. The former fellows began their research careers quickly. At the 12-month follow-up, 16 % reported publishing research results in a peer-reviewed journal and 50 % reported making a presentation at a scientific conference (Leonchuk et al. 2010).

A December 2011 internal NIDA review of the fellowship programs found that former fellows had been principal investigators or principal foreign investigators for 36 NIH grants, funded by NIDA as well as the National Institute on Alcohol Abuse and Alcoholism, National Institute of Allergy and Infectious Diseases, National Institute of Mental Health, and the Fogarty Center. Former NIDA Hubert H. Humphrey, INVEST, and INVEST/CTN Fellows had published nearly 1,000 articles indexed in PubMed, the National Library of Medicine database.

By combining academic study and mentored research, NIDA International Program fellowships can introduce physicians from other countries to drug abuse research careers and help them prepare to take the credentialing examination offered by the International Society of Addiction Medicine.

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Major International Challenges in Addiction Treatment: The Experience of TreatNet and Beyond

148

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Contents

Abstract

One of the three pillars of the UNODC strategy for the prevention and treatment of drug use disorders is the delivery of technical assistance, especially through training. A major initiative in this effort is the Treatnet program. The UNODC Treatnet I global project started in 2005 and was designed to improve the technical capacity of professionals for the delivery of evidence-based drug treatment and

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rehabilitation, along with drug-related HIV/AIDS prevention and care. Treatnet I established a network of 20 resource centers, a comprehensive training curriculum, and a cadre of trainers prepared as expert trainers in the treatment of substance use disorders. From 2009 to 2012, Treatnet II provided advocacy, capacity building, and service improvement in 20 countries in four regions. Using a "training cascade" strategy, Treatnet II provided training to over 11,000 service providers throughout the four regions and the project evaluation indicated a very high rate of satisfaction by the program participants. The current program in this series is the UNODC-WHO Programme on Drug Dependence Treatment and Care. This program has a particular focus on low- and middle-income countries, with the goals of promoting and supporting evidence-based and ethical treatment policies, strategies, and interventions to reduce the burden caused by drug use and dependence. In order to ensure the sustainability of interventions in prevention, treatment, and health/social protection, particularly in low-income countries that need long-lasting and stable support, the continuous provision of significant resources is essential. To provide sustaining support for this effort, the UNODC has called for the creation of a fund to support member states in a systematic and reliable manner.

148.1 Introduction

Substance use disorders are a public health, economic, and security problem in both industrialized and developing countries (Degenhardt and Hall 2006; National Centre for Education and Training on Addiction 2006; UNODC 2003). They are associated with health problems, poverty, violence, criminal behavior, and social exclusion. A large body of science-based evidence concludes that drug dependence is a chronic multifactorial disease affecting the brain and that it is a result of complex mechanisms involving repeated exposure to drugs as well as biological and environmental factors. Both genetic and social elements create risk and resiliency factors that respectively trigger or moderate individual vulnerability to drug use and proneness to further use that may result in dependence.

Prevention and treatment are essential strategies of significant public health importance, as they help prevent drug-related harm and they reduce the severe health and social consequences associated with drug use. Unfortunately, despite the evidence, in many countries, people affected by drug use disorders continue to be stigmatized, criminalized, and deprived of their right to receive adequate, science-based, and humane drug-dependence treatment and care.

148.2 Description

148.2.1 Global Dimension of the Problem

The United Nations Office on Drugs and Crime *World Drug Report* (UNODC 2012) estimates that globally, between 149 and 272 million people (or 3.3–6.1 % of the

population aged 15–64) used illicit substances at least once in the previous year. Although prevalence rates of illicit drug use have remained generally stable over the last decade, the estimate of the number of problem drug users ranges from 15 to 39 million people, equivalent to 0.3–0.9 % of the abovementioned population (UNODC 2012).

148.2.2 UNODC Work in Practice: Treatnet and Beyond

The UNODC's response to its Drug Demand Reduction mandate is based on a three-pillar strategy consisting of:

(a) Advocacy to counteract stigma and discrimination:

The UNODC disseminates information on the benefits of investing in the prevention and treatment of drug use disorders and invites UN member states to consider drug dependence as a preventable and treatable disease within their public health system. To help create the conditions for an evidence-based approach, UNODC programs work with governments' ministries of health and social affairs, as well as justice and interior, in areas including legal and regulatory framework, system and service organization, and financial and human resource investment.

(b) Technical assistance, especially through training:

The UNODC disseminates evidence-based methodologies and capacity-building trainings of professionals in the delivery of services for people who use drugs. By involving country agencies, it tailors the methods toward local conditions, emphasizing the development of country and regional networks of national authorities, academic institutions, and service providers, which then act as resource centers offering sustainable training and dissemination of good practices.

(c) Low-cost, evidence-based, mainstreamed services:

The UNODC promotes a model that envisages two levels of service provision: (i) basic drug-dependence treatment services mainstreamed into the health system, i.e., low cost, decentralized, and thus more accessible and affordable, and (ii) specialized drug-treatment centers at the district/province level that include a multidisciplinary approach for dually diagnosed patients by offering mental health services and inpatient facilities.

A comprehensive approach is used in the scaling-up of treatment services including pharmacological and psychosocial interventions and the building of a rehabilitation-oriented continuum of care ranging from outreach activities to a wide variety of clinical programs.

148.2.2.1 Treatnet I

The UNODC Treatnet I global project, which started in 2005, improved the technical capacity of professionals in the delivery of evidence-based drug-dependence treatment and rehabilitation, along with its important role in drug-related HIV/AIDS prevention and care. Its main approach was the development of knowledge transfer strategies and mutual support between treatment professionals worldwide through a network of drug-dependence treatment centers.

Twenty resource centers were identified through a systematic process aimed at assessing their potential to become leading centers in their respective regions.

For 2 years, the project supported the exchange of knowledge and experience in order to identify best practices and develop four topic-oriented review documents based on state-of-the-art practices and field-based experience on drug-dependence treatment and rehabilitation.

The capacity-building component has been structured on the basis of its own achievements and lessons learned. During the project phase I, a training package was developed through the work of an international consortium of experts on the basis of the training needs identified by the network's members at the time (National Centre for Education and Training on Addiction 2006). The training package is a comprehensive tool consisting of four volumes covering key topics of addiction medicine and aimed at a multidisciplinary audience of drug-treatment service providers.

148.2.2.2 Structure of Treatnet Training Package (UNODC 2007)

Volume A: Screening, Assessment, and Treatment Planning

Module 1:	Screening and brief intervention using the ASSIST
Module 2:	Addiction Severity Index (ASI)
Module 3:	Treatment planning M.A.T.R.S.: utilizing the ASI

Volume B: Elements of Psychosocial Treatment

Module 1:	Drug addiction and basic counseling skills
Module 2:	Motivating clients for treatment and addressing resistance
Module 3:	Cognitive behavioral and relapse prevention strategies

Volume C: Addiction Medications and Special Populations

Module 1:	Addiction basics: alcohol and benzodiazepines; psychostimulants, volatile substances, and cannabis
Module 2:	Opioids: basics of addiction; opiate agonist, partial agonist, and antagonist therapies
Module 3:	Special populations: individuals with co-occurring disorders, women, and young people

Volume D: Administrative Toolkit

Topic 1:	Improving client access and retention (NIATx)
Topic 2:	Clinical supervision techniques
Topic 3:	Program evaluation methods
Topic 4:	Reducing the harm of drug use and dependence and HIV risk reduction

More than 20 trainers were trained to deliver training to staff members at their respective treatment centers. Building upon the human and material resources of phase I, training plans were prepared in phase II to tailor each country's training content to the needs identified through a needs assessment which also included training needs in all participating countries. This process was facilitated by a "Training Coordination Group," consisting of health and academic authorities in

each country. These groups were responsible to organize all training activities under the coordination of the project's regional management team.

Pre- and post-training data was collected and systematized in all countries with training outcomes indicating an increase in knowledge among trainers and practitioners as well as a high level of training satisfaction. The cascaded training of trainers approach facilitated sustainability of knowledge and skills transfer while reaching a high number of professionals.

Treatnet I and II lessons learned and recommendations with respect to the training component can be summarized as follows:

- While the training cascade approach can provide a broad base of knowledge and attitude change, stronger emphasis on follow-up, booster sessions, mentoring, and in-service training would be required for full acquisition of skills.
- Stronger linkages with national academic and training institutions as well as professional networks would facilitate integration of training in professional training programs, sustainability, and ongoing professional exchange and support.
- Additional capacity to train trainers at regional level is required to respond to increasing demand for training.
- While Treatnet I and II assessed trainee satisfaction and knowledge change, an assessment of the training impact on service provision in future training rounds would be required (Tomás-Rosselló et al. 2010).

148.2.2.3 Treatnet II

Following the successful completion of Treatnet I, UNODC developed a scaling-up strategy through a second phase of the project. This phase emphasized intensive involvement and direct participation of national authorities in the creation, consolidation, and expansion of their drug-dependence treatment and care systems. Treatnet II promotes high-quality treatment and care services that are diversified and accessible, including HIV/AIDS prevention and care. It aims to attain a wide range of health and social services for all whose lives are impaired by drug dependence, by working with national counterparts with the ultimate goal to create universal access to evidence-based, comprehensive, and ethical drug-dependence treatment and care.

The project's strategy consists of three pillars:

- Advocacy: Raising awareness that addressing substance use disorders requires a multidisciplinary and comprehensive approach
- Capacity Building: Providing training to health and social service providers using a training-of-trainers approach
- Service Improvement: Creating community-based treatment networks involving health and social services

From 2009 to 2012, Treatnet II was implemented in 22 countries[1] in four regions, where it has contributed to improved quality of drug-dependence treatment services

[1]Brazil, Colombia, Haiti, Nicaragua, Peru, Ivory Coast, Kenya, Nigeria, Mozambique, Sierra Leone, Tanzania, Zambia, Afghanistan, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan, Cambodia, Myanmar, Vietnam, Ukraine.

and increased access to drug treatment for people in need. A major achievement of Treatnet II has been the successful implementation of a knowledge-sharing mechanism called the "training cascade," through which more than 11,000 service providers from various disciplines have received training on evidence-based interventions.

The project has also supported the development and strengthening of drug-treatment services, as well as creating networks of services within a continuum of care. In particular, project support has (1) expanded communities' ability to provide integrated and comprehensive responses to drug use and dependence and/or improve the quality and intensity of services; (2) made drug-dependence treatment and related services more available, accessible, and affordable at selected locations; (3) developed opportunities for social integration and rehabilitation; and (4) supported local organizations, including grassroots, community-based programs and community-based recovery organizations, in linking services and delivering them in a manner consistent with continuum-of-care principles.

The treatment systems for drug use disorders in most countries where Treatnet has been/is being implemented are fragmented and uncoordinated, poorly linked to the overall health system, high threshold, or mostly residential, therefore costly and ineffective, stigmatized, and poorly staffed (numbers and capacity). Given this situation, Treatnet has proposed a community-based treatment "model" referring to a specific integrated model of treatment in the community, which provides a continuum of care from outreach and low-threshold services, through detoxification and stabilization to aftercare and integration, including maintenance pharmacotherapy. The model involves the coordination of a number of health, social, and other nonspecialist services needed to meet the patient's needs. Strong support is also given to the patient's family and the community to address the drug and alcohol problems in their complexity and to ensure efficient and long-term results.

Community-based treatment services are designed to:

- Help patients develop the skills to manage their drug and alcohol dependence and related problems in the community
- Stop or reduce the use of drugs and alcohol
- Respond to a wide range of needs and ensure the best possible outcomes
- Actively involve local organizations, community members, and target populations in the establishment of an integrated network of community-based services in a manner that is empowering
- Facilitate access to a larger number of people in need
- Reduce the need for and use of residential treatment and custodial services for people with drug and alcohol problems

The tasks of promoting, raising awareness, and technically supporting countries toward the implementation of the community-based treatment approach have not been easy or straightforward. In Southeast Asia, community-based treatment services, a new modality for the three participating countries (Cambodia, Myanmar, and Vietnam), have been initiated. This involved a progressive change of attitude toward drug use, people who use drugs, and the understanding of drug dependence as a health disorder. The project has also supported the development of treatment models, guidelines, and standards of care in these three countries. These are a

contributing step in moving away from compulsory centers for drug users, the current dominant response to drug use and dependence in the region, and improving access to HIV prevention. In Cambodia, the Treatnet project has contributed to strengthening the Government's Community Based Drug Treatment Programme (CBTx) through the provision of staffing, technical assistance, capacity building, facilitating meetings among stakeholders, and supporting the delivery of services to people who use drugs at eight sites in Banteay Meanchey province. This has allowed for developing an innovative approach, building relationships and strengthening coordination mechanisms, and planning for future activities with National Government counterparts (at the National Authority for Combating Drugs and the Ministry of Health), subnational authorities (such as the Provincial Drug Control Committee and the Provincial Health Department), and civil society organizations that have partnered with CBTx.

An evaluation conducted in 2011 indicated that Treatnet II training had been useful in increasing the knowledge of staff as well as their use of new approaches toward service provision for drug users. Other findings included:

- More than 95 % of trainees reported that training had been helpful for their work.
- More than 98 % of respondents found the "training packages and manuals useful," and almost 97 % of all therapeutic staff indicated that their relationships with patients had improved as a direct result of the trainings.
- Almost 90 % of respondents reported that their service agency had a better reputation because of the project.
- Three quarters of staff reported observed "positive consequences of Treatnet."
- There were mixed results regarding access to care: the number of individuals waiting for treatment had grown; however, overall, the number of days that patients waited to be admitted fell overall.
- Retention in care improved dramatically: retention in detoxification improved by 42 %, inpatient long-term retention improved by 44 %, outpatient medication-assisted treatment (MAT) improved by 90 %, and outpatient drug-free treatment improved by 145 %.

148.2.3 UNODC-WHO Programme on Drug Dependence Treatment and Care: "Nothing Less than what Is Expected for the Treatment and Care of Any Other Disease"

Building on previous initiatives such as Treatnet I and II, UNODC and the World Health Organization (WHO) launched their Joint Programme on Drug Dependence Treatment and Care in 2009 at the 52nd session of the Commission on Narcotic Drugs in Vienna. With a particular focus on low- and middle-income countries, their goal was to promote and support worldwide, evidence-based, and ethical treatment policies, strategies, and interventions to reduce the burden caused by drug use and dependence. UNODC and WHO have complementary mandates, experience, competencies, and networks and through this program sought to strengthen their collaboration on drug-dependence treatment and care and build

on their respective strengths. As of 2013, the UNODC-WHO Programme is being implemented in 17 countries in five regions (Southeast Europe, Latin America and the Caribbean, Southeast Asia, West Africa, and the Middle East). Its comprehensive approach includes activities at the global, regional, and national level.

148.2.4 Partnership in Action

The UNODC-WHO Programme promotes the recognition of drug dependence as a multifactorial mental health disorder and advocates the need to follow the same quality standards applied to any other chronic disease. The program also seeks to counteract stigma and discrimination against people who suffer from drug dependence. The implementation is guided by the following UNODC-WHO principles of drug-dependence treatment and care[2] (UNODC-WHO 2009):

- Availability and accessibility
- Screening, assessment, diagnosis, and treatment planning
- Evidence-informed drug treatment
- Drug-dependence treatment, human rights, and patient dignity
- Targeting special subgroups and conditions
- Providing addiction treatment within the criminal justice system
- Community involvement and patient-oriented treatment
- Clinical governance of drug-treatment services
- Developing treatment systems: policy development, strategic planning, and coordination of services

148.2.5 Results

Implementation of the UNODC-WHO Programme started in 2010 in Albania, Haiti, Pakistan, and Serbia, building on the existing UNODC Treatnet project and WHO initiatives. The program is currently active in Albania, Serbia, Cambodia, Lao PDR, Vietnam, Brazil, Haiti, Pakistan, as well as countries within Africa, the United Arab Emirates, and the Middle East. Brief summaries of the program's work in Serbia and Haiti follow.

148.2.5.1 Serbia

An existing Coordination Committee was activated at the interministerial and intergovernmental levels, followed by the training of 487 practitioners from four regional centers, support of treatment services at the primary health center level, and the expansion of a primary health-care unit in Belgrade that resulted in a 20 % reduction of patients on waiting lists.

[2]For further details please see https://www.unodc.org/documents/drug-treatment/UNODC-WHO-Principles-of-Drug-Dependence-Treatment-March08.pdf

148.2.5.2 Haiti

After the 2010 earthquake, 27 professionals received training using the Treatnet materials (psychologists, psychiatrists, social assistants, and medical doctors) from the Ministry of Health, APAAC (L'Association pour la Prévention de l'Alcoolisme et autres Accoutumances Chimiques), Mars and Kline Psychiatric Hospital, Defilée de Beudet Hospital, Grace Children's Hospital, Hedo-Haiti, Unique, CONALD (Commission Nationale de Lutte contre la Drogue), and HUEH (Haiti's University and Educational Hospital).

148.2.6 Emerging Themes and Lessons Learned from the Initial Implementation of the UNODC-WHO Programme

Several themes have emerged from the first years of the UNODC/WHO Programme that warrant highlighting:

1. The importance of collaboration between drug control and health agencies at the national and subnational levels.

   In all countries, responsibility for drug-treatment policies and the resources to implement these policies are shared between health and other sectors, including drug control, social welfare, justice, police, and security. Facilitated by the UNODC and WHO links with both the health and crime/security sectors, staff in participating countries are increasingly engaging in multisectoral dialog, collaboration, and decision-making.
2. The challenge of obtaining reliable data on treatment needs and outcomes as basis for sound decision-making on treatment policies.

   Reliable estimates of the size of the population who need services for drug use disorders can be difficult to obtain, even for high-income countries, posing obstacles for countries to plan specific treatment services. Lack of data on available resources, in particular, the organization of services that best match the problem faced by each country, impairs a country's ability to obtain funding from international donors and successfully implement interventions. To assist countries in bridging this gap, WHO and UNODC are developing specific tools such as the Substance Abuse Instrument for Mapping Services (SAIMS), which is used to assess, monitor, and evaluate treatment systems for substance use disorders.
3. The need for standards of care in treatment of drug use disorders.

   In some countries, there are no accepted standards defining treatment of drug use disorders, how it should be provided, and who should provide it. In response, the UNODC-WHO Programme uses a range of methods, including trainings and visits from experts, as well as support for the establishment of a "best practice" treatment facility in the country following UNODC-WHO Principles of Drug Dependence Treatment and Care.
4. The interaction between treatment for people with drug use disorders and criminal justice systems (WHO in press).

   Treatment as an alternative to punishment and other areas of interaction between the criminal justice and health-care systems are often complex but

key areas for intervention. Investing in drug treatment, in preference to the use of criminal or administrative sanctions for people with drug dependence, is not only cost effective but also consistent with human rights principles and the Drug Control Conventions.

5. The coordination of treatment of drug use disorders and treatment of frequent comorbidities.

   Drug dependence is often associated with mental disorders and complicated by physical health problems. In many countries, the epidemics of drug (in particular opioid) injection, HIV, hepatitis B and C, and tuberculosis are highly correlated.

6. The confirmation and reminder of a well-known axiom in the provision of services for substance use disorders: "Not one size fits all."

   Countries differ in drug use extent, patterns, and trends. Legal frameworks, conceptualizations of drug use and dependence, sectors responsible for their management, health system structures, and financing modalities determine the type, quality, appeal, and coverage of services available. Further, the overall perception or level of awareness among the general population, health professionals, and drug-treatment service providers in particular regarding the nature of drug use disorders creates the context in which any initiative for change needs to navigate and influence in order to progress toward a sustainable, comprehensive, human- and science-based response.

7. The main challenge ahead is represented by the perception still firmly rooted in society of drug use and dependence as a moral failure, and therefore a consistent effort is needed to change this attitude and reach an understanding of drug dependence as a chronic health disorder.

148.2.7 International Considerations

Three major debates are occurring regarding the best strategies for dealing with the world drug problem. Long-term polarized discussions about punishing options versus the legalization of drug use have captured public attention, ignoring the fact that people who use and are dependent on drugs are in need of reliable prevention measures and health and social care instead of repressive policy or legalization measures. In addition, the debate about pharmacological versus psychosocial/educational approaches that has dominated the scene in regard to policy for treatment of drug use disorders does not take into account the fact that such a complex disease requires comprehensive and articulated interventions, including differentiated, complementary, and integrated treatment methods. A conflict between advocates of measures to reduce the health and social consequences of drug use and those who favor treatment and recovery has unproductively consumed the time and efforts of policy makers, while neglecting the needs of people who use drugs and patients in all stages of their disease for a full, uninterrupted continuum of care.

148.2.8 Conclusions and the Way Forward

Translating research into practice is a major challenge. The current lack of adequate services and limited access to treatment for people with substance use disorders are compounded by the absence of political prioritization of and commitment to the identification and implementation of solutions to this situation. Because drug dependence is a stigmatized condition, people suffering from drug use disorders are deprived of resources, discriminated against, and excluded from the general health-care mainstream.

UNODC aims to raise awareness among its member states and international organizations regarding the need for creating systematic, large-scale action in the field of prevention and treatment of drug use and dependence; providing care, treatment, and rehabilitation for people who use and are dependent on drugs; reducing the adverse health and social consequences of drug use; integrating supply and demand reduction interventions; and mainstreaming these activities in the broader development of education and health opportunities.

Treatment of drug dependence should be based on effective scientific methods with similar quality standards to those applied in the treatment of any other disease (UNODC 2012). The development of treatment services, starting from low-cost initial-stage facilities, should progress in parallel with other health-care system components – not in isolation. Training for professionals in the field of drug treatment, starting with university curricula for nurses, social workers, counselors, psychologists, medical doctors, and psychiatrists, and building on for those who work in specialized treatment services for drug use disorders, is a critical area, particularly in developing countries.

The UNODC-WHO Programme on Drug Dependence Treatment and Care is a milestone in the development of a comprehensive, integrated health-based approach to drug policy aimed at reducing demand for illicit substances, relieve suffering, and decreasing drug-related harm to individuals, families, communities, and societies. The initiative intends to send a strong message to policy makers to develop services that address drug use disorders in a pragmatic, science-based, and humanitarian way, replacing stigma and discrimination with knowledge, care, recovery opportunities, and reintegration.

148.2.9 The Need for a Large-Scale/High-Level Awareness Process

The international community needs to prioritize the development and implementation of effective interventions to prevent and treat substance use disorders, thus reducing the health and social consequences of these diseases. The first step should be the mobilization of public opinion, the media, and high-ranking politicians for an understanding of substance use disorders as a health condition and stopping the discrimination faced by those who suffer from substance use disorders (UNODC 2010). A large-scale mobilization of civil society, academics, the media, and high-ranking personalities could restore the dignity of people who use and are dependent

on drugs, protect the human rights of individuals vulnerable to substance use disorders, and contribute to reducing the burden of substance use disorders on communities' health, security, and economy.

Such a mobilization should walk hand in hand with the adoption of effective strategies tested through reliable trials and/or national experiences and adaptation of these strategies to various sociocultural environments. Cost-effective prevention and treatment tools exist and should be systematically used, along with measures of outreach, health-care, and social services that alleviate the consequences of substance use and dependence.

148.2.10 A Permanent Fund

Following political commitment to an understanding of substance-related disorders as a health condition and to the implementation of evidence-based interventions, the development and maintenance of responses in prevention, treatment, and health/social protection in low-income countries require at this point long-lasting and stable support. Therefore, the continuous provision of significant resources is essential. UNODC has called for the creation of a fund to support member states in a systematic and reliable manner. The fund should operate for 10 years, providing grants for training and improvement of services and supporting low-income countries in building their prevention, treatment, and health/social protection systems, which, in the long term, should become self-sustainable. For this purpose, chiefs of state and governments should urgently consider this issue at the next meeting of the G20.

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WHO (in press) Interaction between the health care and criminal justice system for people with drug use disorders, humane and effective examples from around the world
WHO (in press) WHO district clinical manual (chapter on substance abuse)
WHO controlled medicine database. www.who.int/hiv/amds/ControlledMedicineDatabase.xls

Pain Education Curriculum in Medical Schools

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Bridin Murnion

Contents

Abstract

Increasing prescription opioid misuse defines a need for medical practitioners to have pain assessment and management skills. Pain education should commence in undergraduate programs. This chapter describes pain curricula, focussing on the IASP curriculum, and describes methods of delivery of pain education.

149.1 Introduction

There are few human experiences as universal as that of pain. It is the presenting symptom in 70 % of emergency department presentations. Eighty percent of postoperative patients complain of pain (Vadivelu et al. 2012). Approximately 20 % of the population have chronic non-cancer pain, and 30 % of these are unable to function in their work role (IASP 2013). Not only does this cause a personal burden of suffering and financial hardship, there is a societal economic impact as well.

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Pain management is a diverse discipline encompassing acute operative, acute nonoperative, chronic non-cancer pain and cancer pain. Pain management is multimodal and includes medications, interventional procedures, psychological approaches, and physical strategies. Effective pain management requires skills from many disciplines such as medical, nursing, physiotherapy, occupational therapy, and psychology.

In the last decade there has been an explosion in opioid prescription for pain, with a concomitant explosion in prescription opioid misuse. In response to this increase in prescription opioid misuse, there has been advocacy for enhancing healthcare practitioners' skills in recognizing and managing opioid misuse (UNODC 2011). There has also been increasing recognition that all healthcare practitioners, not just addiction specialists, need adequate pain management skills to reduce inappropriate opioid prescribing and improve pain management. The addiction specialsit has a particular interest as not only is opioid misuse increasingly an iatrogenic problem, but also many of the patients with prescription opioid misuse have underlying chronic pain which needs to be addressed concurrently and may also have intercurrent acute pain. The assessment and management of acute pain in the context of opioid dependence and chronic pain presents specific challenges.

The evolution of pain medicine as a specialty has allowed some focussed development of educational initiatives, both at undergraduate and postgraduate level. There is widespread acceptance that most medical practitioners should have pain management skills and that responsibility and skills for pain management cannot rest solely with pain specialists. Expert consensus agrees that pain education should begin in medical schools (IASP 2013). This chapter will provide an overview of current medical school pain curricula, the resources available, and some curriculum delivery models.

149.2 Curricular Features

Over the last 20 years, there has been significant progress in our understanding of the science of pain, both acute and chronic (IASP 2013). This has occurred in both basic and clinical science. Our understanding of the neuroanatomy and neuropharmacology of pain has expanded dramatically. We have enhanced knowledge of clinical treatment paradigms, whether pharmacological, surgical, psychological, or physical-based therapies. With the advent of computerized tomography, magnetic resonance imaging, and positron emission tomography, our capacity to image both experimentally and in routine clinical practice has advanced beyond what could have been imagined 30 years ago.

The International Association for the Study of Pain (IASP) is the professional body for scientists, educators, and clinicians working or researching in pain. Membership is open to any individual working or researching in pain and is drawn from over 130 countries. IASP defines its role as to support and advocate for pain research and practice, such that pain management is improved globally. There are a number of local chapters throughout the world and a developing countries' project (IASP 2013).

Some 25 years ago, the IASP recognized the need for and developed an undergraduate/prelicensure pain curriculum. Since that time, there have been a number of revisions, the most recent in 2012. This is available for free download on the IASP website (IASP 2013).

Despite our expanding knowledge and a freely available curriculum, there has not been paralleled by increased education about pain in medical school curricula.

Mezei and Murinson (2011) reviewed the curricula of 117 medical schools in Canada and the USA between 2009 and 2010 and identified that 80 % of medical schools in the USA and 92 % in Canada have some requirement for pain education. However, dedicated time was limited although Canada fared better than the USA. Curriculum content was inadequate and much of the core undergraduate curriculum of the International Association for the Study of Pain was not covered adequately if at all. The authors conclude that pain education in medical schools in North America is "limited and fragmentary."

Vadivelu et al. (2012) have reviewed curriculum across a number of different countries and regions. In medical schools in the UK, an average of 13 h is allocated for pain teaching and, similar to the North American experience, is considered inadequate and fragmented. Alarmingly veterinary science and physiotherapy have the greatest time allocation for pain education. Elsewhere in Europe, medical schools in Finland provide reasonable coverage of the IASP curriculum, although the delivery of this curriculum is perhaps suboptimal. Undergraduate pain education appears to be in a parlous state in the developing world. Although there are very limited data looking at the extent of pain education in these countries, the data that are available suggest very limited undergraduate exposure, poor understanding of the risks of opioid analgesics medications for treatment of pain, low prioritization of pain, and inadequate outcomes in pain treatment (Vadivelu et al. 2013).

Thus, it is evident that despite the high prevalence of pain in the population, the clear need for all medical practitioners to have pain management skills, and a readily available curriculum, pain does not have adequate coverage in most medical school curricula. Likely reasons for this include resources, both human and educational, busy curricula with multiple competing demands, and lack of coordination of fragmented pain teaching. Pain is a relatively new specialty so may well be fighting with more established groups for curriculum space. In addition, having adequate pain management skills is important in most areas of medicine (e.g., surgery, palliative care, pediatrics, geriatrics). Integration of pain teaching across multiple specialties is challenging.

149.2.1 IASP Curriculum and Its Derivatives

The IASP has developed a number of curricula for the various craft groups within healthcare (e.g., medicine, dentistry, nursing). In addition, in 2012, an interdisciplinary curriculum was developed. The IASP recognizes that changing medical school curricula is complex. One of the goals in developing the medical curriculum was to try and engage curriculum leaders in discussion round the importance of

adequate pain education and to give a guideline as to what should be included (IASP 2013). In this context, both the medical school and the interdisciplinary curriculum warrant further examination.

149.2.2 Medicine Curriculum

The prelicensure medicine curriculum is one of the seven uniprofessional curricula developed by IASP. The objectives of the curriculum outline for medicine are that after completing the course, the student should appreciate the importance of pain medicine in clinical practice, understand the basic science of pain, be able to diagnose in acute and chronic pain effectively, understand the biopsychosocial model of pain and its management, understand pharmacological treatment, and begin to develop the capacity to work in the multidisciplinary team of pain medicine.

There are four key domains of the curriculum which are:

1. Multidimensional nature of pain
2. Pain assessment and measurement
3. Management of pain
4. Clinical conditions

Each of these domains is further expanded. Domain 3, for example, includes subheadings of general principles of management, clinical pharmacology, neurostimulation, psychological therapies, nerve blocks, surgical techniques, and physical therapies. These subheadings are further elaborated, e.g., surgical techniques are expanded to nerve decompression, neurosurgical, and orthopaedic techniques.

The IASP suggests that the curriculum is delivered as basic, clinical, and social science early in the medical degree, with a pain medicine course later in the degree. Beyond that it makes no recommendations regarding delivery, nor does it supply educational resources. It however directs the reader to the German model as an example of content delivery (IASP 2013).

The European Federation of IASP Chapters, EFIC, provide a comprehensive medical school curriculum developed from the IASP curriculum. This provides a clear curriculum framework, guiding principles, curriculum domains, and very detailed educational objectives. A detailed timetable for delivering the content is provided. This again is based on the German model and is updated biannually (EFIC 2013).

149.2.3 Interprofessional Curriculum

Pain is multidimensional and treatment of pain is optimally provided in multidisciplinary teams. In recognition of this, in 2012 IASP published an interprofessional curriculum (IASP 2013). This was developed over a number of years by an expert group from a variety of health science backgrounds. The curriculum was developed in a manner to ensure that it was relevant to all professions and cross-referenced to

the individual healthcare professional curriculum to ensure inclusion of common themes. It was then sent for further evaluation through review by members of the special interest group in education of the IASP. It is anticipated that further development will occur iteratively as feedback after use will be generated to assist in further refining the curriculum.

One of the major goals of the interprofessional curriculum is to facilitate shared learning and enhance understanding of roles and competencies of the different disciplines within the pain management team. While all disciplines should understand the core components, the depth of understanding will be defined by the professional group to which an individual student belongs.

As an implementation strategy, the IASP suggests core lectures with small group work around common themes. It advocates that students return to their "home" discipline for curriculum areas that require specific focus for their professional group.

The four key domains of the curriculum remain the same as in the uniprofessional curricula, i.e., the multidimensional nature of pain, pain assessment and measurement, management of pain, and clinical conditions.

The objectives of the curriculum, not unsurprisingly, are somewhat different. It is expected that the student completing the curriculum should understand methods of pain assessment and treatment common to all health professionals, as well as have an understanding of the common misbeliefs. They should understand the complex multidimensional nature of pain and its impact on patients and families. The student should understand how all professions individually and collaboratively develop and provide pain management plans and how outcomes of this are monitored. It is also expected that they have a sophisticated understanding of the individual and societal issues around inadequate pain treatment.

This curriculum is much more comprehensive and for the most part more explicit than the uniprofessional medical curriculum. Looking again at domain 3 "management of pain," this is subdivided into:

1. Goals of pain management
2. Pain management planning decisions
3. Treatment considerations
4. Pharmacological methods
5. Non-pharmacological methods
6. Evaluation of outcomes

The sub-domain 2 of pain management planning decisions in the interprofessional curriculum is illustrative of the differences between the two curricula. This sub-domain identifies as core content that treatment plans should be developed and implemented as an interprofessional or multiprofessional team. Patients and families should be involved in setting goals which are realistic and clear and that they should have information regarding treatment options and side effects. Treatment should be multimodal where appropriate. Pain management planning decisions are not included in the uniprofessional medical curriculum, although understanding of the multidisciplinary pain clinic, psychological interventions, and physical therapies are included in different domains.

While the subheading of non-pharmacological methods includes surgical techniques, these are not specifically defined as nerve decompression, neurosurgical, and orthopaedic techniques that are identified as core content for the medicine curriculum.

The IASP also offers education grants to countries in the developing world for the development of pain education in medical schools. EFIC can award financial assistance to eastern European countries for pain curriculum implementation, recognizing that specific local factors may need to be addressed during implementation.

Most recently, interdisciplinary pain competencies have been proposed (Fishman et al 2013). An expert working party derived 21 competencies over four domains that prelicensure students across healthcare disciplines could be expected to achieve. The four domains are again the multidimensional nature of pain, pain assessment and measurement, pain management, and clinical conditions. The developers' intent is that these competencies are used to define and refine pain curricula.

149.2.4 Curriculum Delivery

A number of methods of delivering pain education are described. Murinson et al. (2011) describe the process and outcomes of an intensive 4-day course in pain medicine to first year medical students at Johns Hopkins University. The School of Medicine underwent curriculum redesign, providing an opportunity for integration of pain education. Pain is a "horizontal strand" that continues throughout the 4-year course. The 4-day course during first year is the foundation for subsequent learning. This is comprised of some didactic lecture teaching, but predominantly delivered as small group discussions, team-based learning, and laboratory sessions. The assessment tasks, done on day 4 of the short course, include multiple choice questions, an assessment task, and a short pain portfolio. The goal of the portfolio was to enhance understanding of the emotional aspects of pain. Outcome assessment identified learner satisfaction and knowledge acquisition and good participation in the portfolio exercise. However, course implementation was labor intensive requiring over 60 staff for delivery.

Hartrick et al. (2012) integrate pain basic science into first year pharmacology teaching, using pain neuroscience and pharmacology to illustrate principals of pharmacology (e.g., buprenorphine as a partial agonist, patient-controlled analgesia, and volume of distribution).

Since 2002, the University of Toronto has iteratively developed an interfaculty pain curriculum with students from medicine, dentistry, pharmacy physiotherapy, and occupational therapy (Hunter et al. 2008). A number of settings such as large groups and small groups are used to deliver content. Groups may be uniprofessional, multiprofessional, or interprofessional. Written material has been developed to support both students and facilitators. Prior to participation, facilitators attend a 3 h training workshop. Outcomes were measured by assessing

students' pain knowledge and beliefs pre- and post course, assessment of content and processes via a questionnaire to students and facilitators, and the assessment of the students' ability to develop a comprehensive pain management plan. The course performed well in all domains. Again, this course is human resource intensive.

149.3 Conclusion

It is evident that excellent uniprofessional and interprofessional pain curricula with comprehensive content are freely available. A significant barrier is the failure to adequately include pain or allocate appropriate time in medical school curricula. Continuing advocacy from IASP, local chapters and postgraduate bodies are needed to improve this. Other challenges include effective implementation in countries with limited resources and how to integrate pain education into other specialties in a curriculum. Ensuring pain curricula are delivered in a manner that allows development of the humanistic aspects of pain management such as empathy and compassion, rather than just acquisition of knowledge and skills, is important. These problems, however, are not insurmountable. It is to be hoped that with the continuing advocacy and commitment of IASP, its local chapters, postgraduate bodies, pain academics, and consumer groups, pain medicine will continue to gain momentum.

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